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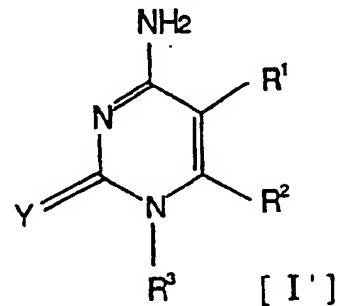
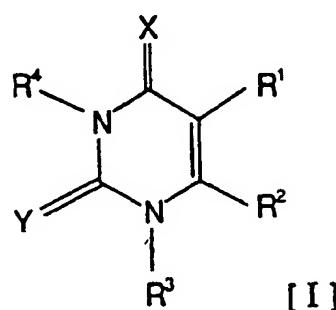
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(54) 6-Substituted acacyclopyrimidine nucleoside derivatives and antiviral agent containing the same as active ingredient thereof.

(57) A 6-substituted acacyclopyrimidine nucleoside derivative represented by the following general formula I or I':



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wherein R<sup>1</sup> represents a hydrogen atom, halogen atom, alkyl, cycloalkyl, alkenyl, alkynyl, alkylcarbonyl, arylcarbonyl, arylcarbonylalkyl, arylthio or aralkyl group;  
 R<sup>2</sup> represents an arylthio, alkylthio, cycloalkylthio, arylsulfinyl, alkylsulfinyl, cycloalkylsulfinyl, alkenyl, alkynyl, aralkyl, arylcarbonyl, arylcarbonylalkyl or aryloxy group, those groups optionally substituted by one or more of substituents selected from a halogen atom, alkyl, halogenated alkyl, alkoxy, hydroxyl, nitro, amino, cyano and

acyl groups:

R<sup>3</sup> represents a hydrogen atom, methyl, branched alkyl or -CH<sub>2</sub>-Z-(CH<sub>2</sub>)<sub>n</sub>-R<sup>5</sup> group where R<sup>5</sup> represents a hydrogen atom, halogen atom, hydroxyl, heterocyclic carbonyloxy, formyloxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, aralkylcarbonyloxy, arylcarbonyloxy, azido, alkoxy carbonyloxy, N-alkylcarbamoyloxy, N-arylcarbamoyloxy, N-alkylthiocarbamoyloxy, N-arylthiocarbamoyloxy, alkoxy, aralkyloxy, branched alkyl, cycloalkyl or aryl group, the alkoxy carbonyloxy to aryl groups mentioned above as R<sup>5</sup> optionally substituted by one or more substituents selected from a halogen atom, aryl, alkyl, alkoxy and halogenated alkyl groups, Z represents an oxygen, sulfur atom or methylene group, and n represents 0 or an integer of 1 to 5.

R<sup>4</sup> represents a hydrogen atom, alkyl or aralkyl group,

X represents an oxygen or sulfur atom,

Y represents an oxygen or sulfur atom,

provided that when R<sup>4</sup> and Z represent a hydrogen atom and oxygen atom respectively in the formula I R<sup>5</sup> does not represent a hydroxyl group,

or a pharmaceutically acceptable salt thereof, and an antiviral agent containing the derivative or the salt thereof as an active ingredient.

**6-SUBSTITUTED ACYCLOPYRIMIDINE NUCLEOSIDE DERIVATIVES AND ANTIVIRAL AGENT CONTAINING  
THE SAME AS ACTIVE INGREDIENT THEREOF**

**FIELD OF THE INVENTION**

The present invention relates to novel 6-substituted acyclopyrimidine derivatives and antiviral agents  
5 containing the derivative as the active ingredients.

**BACKGROUND OF THE INVENTION**

10 Infectious diseases caused by human acquired immunodeficiency virus (HIV), which is a type of retrovirus, have recently become a serious social problem. A compound of 3'-deoxy-3'-azidothymidine is known as a nucleoside compound used in the clinical treatment for diseases caused by HIV-infection. However, this compound has side-effects since it also exhibits considerable strong toxicity in the host cells.

15 Although some 2',3'-dideoxyribonucleosides are known as nucleoside compounds exhibiting an antiviral activity, it is still necessary to develop a substance possessing a higher activity and lower toxicity to the host cell (Hiroaki Mitsuya, Bodily Defense, Vol. 4, pp.213 - 223 (1987)).

20 On the other hand, various acyclonucleoside compounds have been synthesized since Acyclovir (acycloguanosine) was developed as an antiviral substance effective against herpes virus (C.K. Chu and S.J. Culter, J. Heterocyclic Chem., 23, p.289 (1986)). However, no acyclonucleoside compound having a sufficient activity especially against retroviruses has yet been discovered.

25 We have focussed our attention on 6-substituted acyclopyrimidine nucleoside compounds and have synthesized various novel 6-substituted acyclopyrimidine nucleoside derivatives and screened those compounds to detect effective antiviral agents, especially to the retrovirus, in order to provide antiviral agents exhibiting an effective activity particularly against retroviruses.

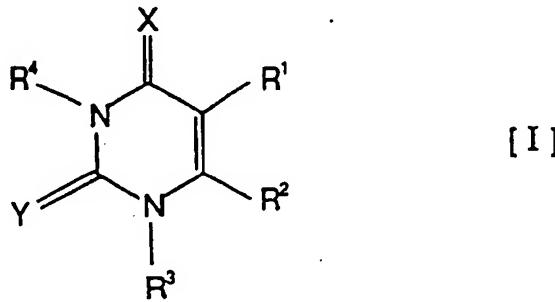
30 Some 6-substituted acyclopyrimidine nucleoside compounds such as 6-fluoro substituted derivatives, 6-alkylamino substituted derivatives (DD-A-232492) and 6-methyl substituted derivatives (C.A. 107, 129717w (1987)) are known; however, the antiviral activity of these compounds has not been described.

35 As a result of our researches for compounds exhibiting an effective antiviral activity, particularly anti-retroviral activity, we found that specific 6-substituted pyrimidine nucleoside compounds according to the invention satisfy the above demand to achieve the present invention.

**SUMMARY OF THE INVENTION**

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The present invention concerns 6-substituted acyclopyrimidine nucleoside derivatives represented by the following general formula I;



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wherein R<sup>1</sup> represents a hydrogen atom, halogen atom, alkyl, cycloalkyl, alkenyl, alkynyl, alkylcarbonyl, arylcarbonyl, arylcarbonylalkyl, arylthio or aralkyl group;

R<sup>2</sup> represents an arylthio, alkylthio, cycloalkylthio, arylsulfinyl, alkylsulfinyl, cycloalkylsulfinyl, alkenyl,

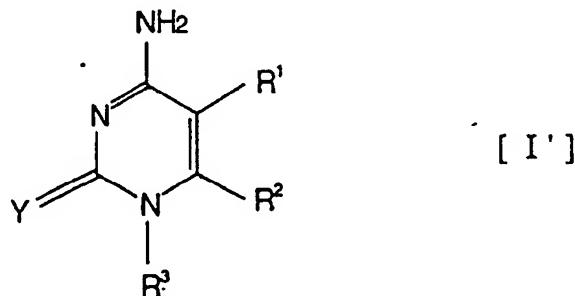
alkynyl, aralkyl, arylcarbonyl, arylcarbonylalkyl or aryloxy group, those groups optionally substituted by one or more of substituents selected from a halogen atom, alkyl, halogenated alkyl, alkoxy, hydroxyl, nitro, amino, cyano and acyl groups;

- 5 R<sup>3</sup> represents a hydrogen atom, methyl, branched alkyl or -CH<sub>2</sub>-Z-(CH<sub>2</sub>)<sub>n</sub>-R<sup>5</sup> group where R<sup>5</sup> represents a hydrogen atom, halogen atom, hydroxyl, heterocyclic carbonyloxy, formyloxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, aralkylcarbonyloxy, aryloxy, azido, alkoxy, carbonyloxy, N-alkylcarbamoyloxy, N-arylcarbamoyloxy, N-alkylthiocarbamoyloxy, N-aryltiocarbamoyloxy, alkoxy, aralkyloxy, branched alkyl, cycloalkyl or aryl group, the alkoxy, carbonyloxy to aryl groups mentioned above as R<sup>5</sup> optionally substituted by one or more substituents selected from a halogen atom, aryl, alkyl, alkoxy and halogenated alkyl groups,
- 10 10 Z represents an oxygen, sulfur atom or methylene group, and n represents 0 or an integer of 1 to 5.
- R<sup>4</sup> represents a hydrogen atom, alkyl or aralkyl group,
- X and Y represent an oxygen or sulfur atom independently, provided that when R<sup>4</sup> and Z represent a hydrogen atom and oxygen atom respectively R<sup>5</sup> does not represent a hydroxyl group, or the following general formula I' :

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wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and Y have the same meanings as defined for the formula I above, pharmaceutically acceptable salts thereof and antiviral agents containing the derivative or the salt thereof as an active ingredient.

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#### DETAILED DESCRIPTION OF THE INVENTION

35

The 6-substituted acyclopyrimidine nucleoside derivatives according to the invention are represented by the general formula I or I'.

40

The group of R<sup>1</sup> represents a hydrogen atom; halogen atom such as chlorine, iodine, bromine and fluorine; alkyl group such as methyl, ethyl, n-propyl, i-propyl- and n-butyl; cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; alkenyl group such as vinyl, propenyl, butenyl, phenylvinyl, bromovinyl, cyarovinyl, alkoxy, carbonylvinyl and carbamoylvinyl; alkynyl group such as ethynyl, propynyl and phenylethynyl; alkylcarbonyl group such as acetyl, propionyl, and i-butyryl; arylcarbonyl group such as benzoyl and naphthoyl; arylcarbonylalkyl group such as phenacyl; arylthio group such as phenylthio, tolylthio and naphthylthio; or aralkyl group such as benzyl.

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The group of R<sup>2</sup> represents an arylthio group such as phenylthio and naphthylthio; alkylthio group such as methylthio, ethylthio, propylthio, butylthio and pentylthio; cycloalkylthio group such as cyclopentylthio, cyclohexylthio and cycloheptylthio; arylsulfinyl group such as phenylsulfinyl; alkylsulfinyl group such as methylsulfinyl, ethylsulfinyl and butylsulfinyl; cycloalkylsulfinyl group such as cyclopentylsulfinyl and cyclohexylsulfinyl; alkenyl group such as vinyl, propenyl and phenylvinyl; alkynyl group such as ethynyl, propynyl and phenylethynyl; aralkyl group such as benzyl; arylcarbonyl group such as benzoyl; arylcarbonylalkyl group such as phenacyl; or aryloxy group such as phenoxy, and those groups may be optionally substituted by one or more of substituents selected from a halogen atom such as chlorine, bromine, fluorine and iodine, alkyl group such as methyl, ethyl, propyl, butyl and pentyl, a halogenated alkyl group such as trifluoromethyl, alkoxy group such as methoxy, ethoxy, propoxy and butoxy, hydroxyl group, nitro group, amino group, cyano group and acyl group such as acetyl.

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The group of R<sup>3</sup> represents a hydrogen atom, methyl group, branched alkyl group such as i-propyl and t-butyl or -CH<sub>2</sub>-Z-(CH<sub>2</sub>)<sub>n</sub>-R<sup>5</sup> group where R<sup>5</sup> represents a hydrogen atom; halogen atom such as fluorine, chlorine, iodine and bromine; hydroxyl group; heterocyclic carbonyloxy group such as nicotinoyloxy;

formyloxy group; optionally branched alkylcarbonyloxy group such as acetoxy, proponyloxy, n-butyryloxy, i-butyryloxy, valeryloxy, hexanoyloxy, heptanoyloxy and decanoxyloxy; cycloalkylcarbonyloxy group such as cyclohexylcarbonyloxy; aralkylcarbonyloxy group such as benzylcarbonyloxy; arylcarbonyloxy group such as benzyloxy, toluoylcarbonyloxy and naphthoylcarbonyloxy group; azido group; alkoxy carbonyloxy group such as methoxycarbonyloxy, ethoxycarbonyloxy, n-propoxycarbonyloxy, i-propoxycarbonyloxy, n-butoxy carbonyloxy and t-butoxy carbonyloxy group, optionally substituted by one or more substituents selected from a halogen atom such as fluorine, chlorine, bromine and iodine, aryl group such as phenyl, toluyl and naphthyl, alkyl group such as methyl, ethyl, n-propyl, i-propyl, n-butyl and t-butyl, alkoxy group such as methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy and t-butoxy and halogenated alkyl group such as trifluoromethyl; N-alkylcarbamoyloxy group such as N-methylcarbamoyloxy, N-ethylcarbamoyloxy, N-propylcarbamoyloxy, N-butylcarbamoyloxy and N-pentylcarbamoyloxy, optionally substituted by one or more substituents selected from a halogen atom such as fluorine, chlorine, bromine and iodine, aryl group such as phenyl, toluyl and naphthyl, alkyl group such as methyl, ethyl, n-propyl, i-propyl, n-butyl and t-butyl, alkoxy group such as methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy and t-butoxy and halogenated alkyl group such as trifluoromethyl; N-arylcaramoyloxy group such as N-phenylcarbamoyloxy and N-tolylcarbamoyloxy, optionally substituted by one or more substituents selected from a halogen atom such as fluorine, chlorine, bromine and iodine, aryl group such as phenyl, toluyl and naphthyl, alkyl group such as methyl, ethyl, n-propyl, i-propyl, n-butyl and t-butyl, alkoxy group such as methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy and t-butoxy and halogenated alkyl group such as trifluoromethyl; N-alkylthiocaramoyloxy group such as N-methylthiocaramoyloxy, N-ethylthiocaramoyloxy, N-propylthiocaramoyloxy, N-butylthiocaramoyloxy and N-pentylthiocaramoyloxy, optionally substituted by one or more substituents selected from a halogen atom such as fluorine, chlorine, bromine and iodine, aryl group such as phenyl, toluyl and naphthyl, alkyl group such as methyl, ethyl, n-propyl, i-propyl, n-butyl and t-butyl, alkoxy group such as methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy and t-butoxy and halogenated alkyl group such as trifluoromethyl; N-aryltiocaramoyloxy group such as N-phenylthiocaramoyloxy and N-tolylthiocaramoyloxy, optionally substituted by one or more substituents selected from a halogen atom such as fluorine, chlorine, bromine and iodine, aryl group such as phenyl, toluyl and naphthyl, alkyl group such as methyl, ethyl, n-propyl, i-propyl, n-butyl and t-butyl, alkoxy group such as methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy and t-butoxy and halogenated alkyl group such as trifluoromethyl; alkoxy group such as methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, t-butoxy, n-pentyloxy and n-hexyloxy group, optionally substituted by one or more substituents selected from a halogen atom such as fluorine, chlorine, bromine and iodine, aryl group such as phenyl, toluyl and naphthyl, alkyl group such as methyl, ethyl, n-propyl, i-propyl, n-butyl and t-butyl, alkoxy group such as methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy and t-butoxy and halogenated alkyl group such as trifluoromethyl; branched alkyl group such as i-propyl, i-butyl, sec-butyl, t-butyl, i-heptyl and i-hexyl, optionally substituted by one or more substituents selected from a halogen atom such as fluorine, chlorine, bromine and iodine, aryl group such as phenyl, toluyl and naphthyl, alkyl group such as methyl, ethyl, n-propyl, i-propyl, n-butyl and t-butyl, alkoxy group such as methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy and t-butoxy and halogenated alkyl group such as trifluoromethyl; cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, optionally substituted by one or more substituents selected from a halogen atom such as fluorine, chlorine, bromine and iodine, aryl group such as phenyl, toluyl and naphthyl, alkyl group such as methyl, ethyl, n-propyl, i-propyl, n-butyl and t-butyl, alkoxy group such as methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy and t-butoxy and halogenated alkyl group such as trifluoromethyl; or aryl group such as phenyl, optionally substituted by one or more substituents selected from a halogen atom such as fluorine, chlorine, bromine and iodine, aryl group such as phenyl, toluyl and naphthyl, alkyl group such as methyl, ethyl, n-propyl, i-propyl, n-butyl and t-butyl, alkoxy group such as methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy and t-butoxy and halogenated alkyl group such as trifluoromethyl, and Z represents an oxygen, sulfur atom or methylene group, and n represents 0 or an integer of 1 to 5.

50 R<sup>4</sup> represents a hydrogen atom; optionally branched alkyl group such as methyl, ethyl, n-propyl, i-propyl, n-butyl and t-butyl; or aralkyl group such as benzyl.

55 X and Y represent oxygen or sulfur atom independently.

In the above formula I, when R<sup>4</sup> and Z represent a hydrogen atom and oxygen atom respectively, R<sup>5</sup> does not represent a hydroxyl group.

The preferred compounds according to the invention have R<sup>1</sup> of a hydrogen atom, halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl group or C<sub>2</sub> to C<sub>5</sub> alkenyl group, particularly C<sub>1</sub> to C<sub>5</sub> alkyl group; R<sup>2</sup> of C<sub>6</sub> to C<sub>10</sub> arylthio group, C<sub>3</sub> to C<sub>10</sub> cycloalkylthio group or C<sub>7</sub> to C<sub>11</sub> aralkyl group, particularly C<sub>6</sub> to C<sub>10</sub> arylthio, C<sub>3</sub> to C<sub>10</sub> cycloalkylthio or C<sub>7</sub> to C<sub>11</sub> aralkyl group, optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and nitro groups; R<sup>3</sup> of a hydrogen atom, methyl or -CH<sub>2</sub>-Z-

$(CH_2)_n\text{-}R^5$  group where  $R^5$  represents a hydrogen atom, halogen atom, hydroxyl, heterocyclic carbonyloxy,  $C_2$  to  $C_{11}$  alkylcarbonyloxy,  $C_4$  to  $C_{10}$  cycloalkylcarbonyloxy,  $C_8$  to  $C_{12}$  aralkylcarbonyloxy,  $C_7$  to  $C_{13}$  arylcarbonyloxy,  $C_2$  to  $C_{11}$  alkoxy carbonyloxy,  $C_8$  to  $C_{10}$  aralkyloxycarbonyloxy,  $C_2$  to  $C_8$  N-alkylcarbamoyloxy,  $C_7$  to  $C_{13}$  N-arylcaramoyloxy,  $C_2$  to  $C_8$  N-alkylthiocarbamoyloxy,  $C_7$  to  $C_{13}$  N-aryliocarbamoyloxy,  $C_1$  to  $C_{10}$  alkoxy,  $C_7$  to  $C_{13}$  aralkyloxy, azido,  $C_3$  to  $C_5$  branched alkyl,  $C_5$  to  $C_7$  cycloalkyl or  $C_6$  to  $C_{10}$  aryl group optionally substituted by one or more substituents selected from a halogen atom, aryl, alkyl, alkoxy and halogenated alkyl groups,  $Z$  represents an oxygen, sulfur atom or methylene group, and  $n$  represents 0 or an integer of 1 to 5;  $R^4$  of a hydrogen atom,  $C_1$  to  $C_{13}$  alkyl or  $C_7$  to  $C_{11}$  aralkyl group;  $X$  of an oxygen or sulfur atom; and  $Y$  of an oxygen or sulfur atom; provided that when  $R^4$  and  $Z$  represent a hydrogen atom and oxygen atom respectively  $R^5$  does not represent hydroxyl group.

Examples of the preferred compounds according to the present invention are listed in Table 1 below.

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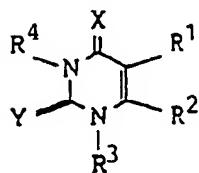
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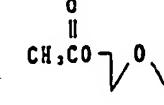
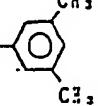
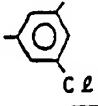
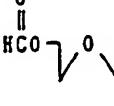
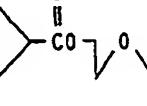
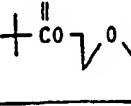
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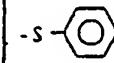
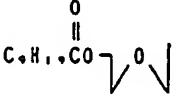
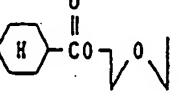
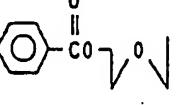
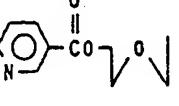
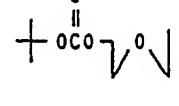
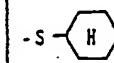
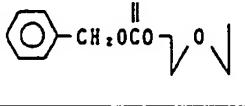
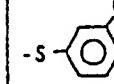
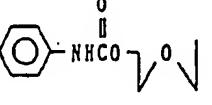
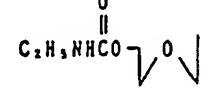
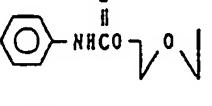
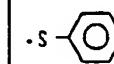
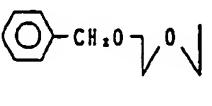
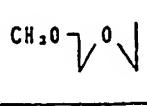
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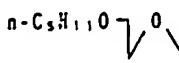
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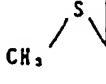
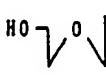
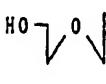
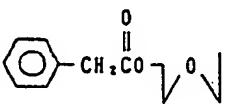
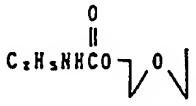
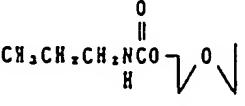
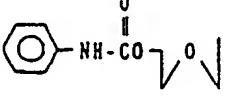
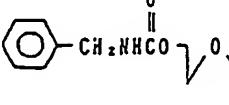
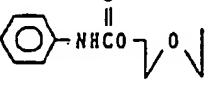
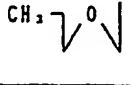
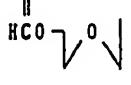
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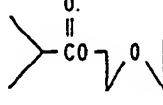
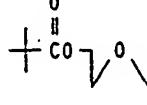
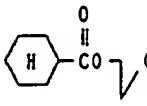
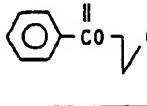
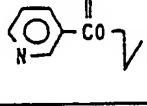
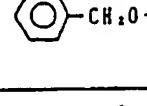
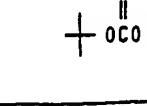


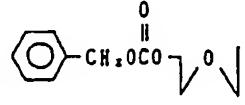
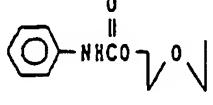
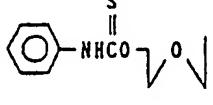
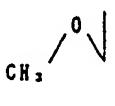
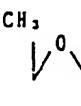
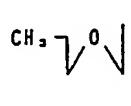
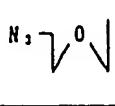
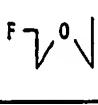
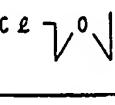
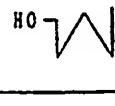
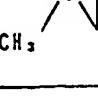
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15 1	-CH <sub>3</sub>	-S- 		-H	0	S	112 113
20 2	-	-	-	-	-	0	112 113
25 3	-	-S- 	-	-	-	-	155.5 156.6
30 4	-	-	-	-	-	S	144 145
35 5	-	-S- 	-	-	-	0	132 133
40 6	-	-CH <sub>2</sub> - 	-	-	-	-	100 115
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55 9	-	-		-	-	-	99 102

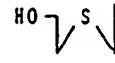
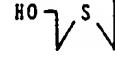
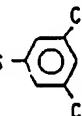
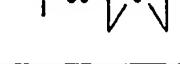
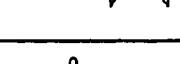
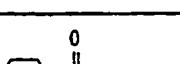
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20	13	"	"		"	"	"	139 140
25	14	"	"		"	"	"	115 119
30	15	"	-S- 		"	"	"	95 97
35	16	"	-S- 		"	"	"	175 176
40	17	"	"		"	"	"	148 150
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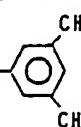
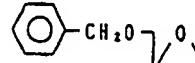
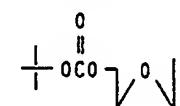
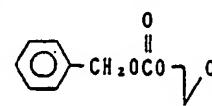
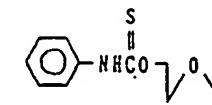
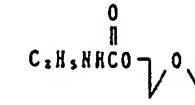
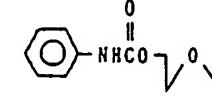
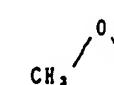
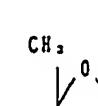
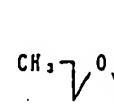
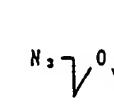
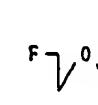
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15	23	"	"	CH <sub>3</sub> 	"	"	"	133 134
20	24	"	"	N <sub>2</sub> 	"	"	"	91 92
25	25	"	"	F 	"	"	"	136 137
30	26	"	"	C <sub>2</sub> 	"	"	"	123 124
35	27	"	"	H	"	"	"	238 242
40	28	"	"	CH <sub>3</sub>	"	"	"	229 230
45	29	"	"	C <sub>2</sub> H <sub>5</sub>	"	"	"	158 160
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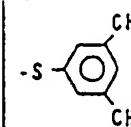
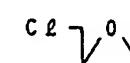
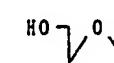
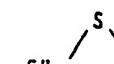
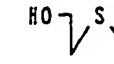
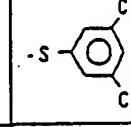
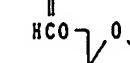
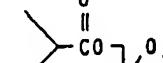
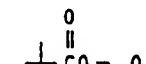
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10	33	"	"		-CH <sub>2</sub> - 	"	"	Oil
15	34	"	"		-CH <sub>3</sub>	"	"	74 75
20	35	"	"		-H	"	"	
25	36	"	"		"	"	"	
30	37	"	"		"	"	"	
35	38	"	"		"	"	"	
40	39	"	"		"	"	"	
45	40	"	"		"	"	"	
50	41	"	"		"	"	"	136 138
55	42	"	"		"	"	S	

5	43	-CH <sub>3</sub>	-S- 	$\text{CH}_3\text{CO}-\text{V}^0\backslash$	-CH <sub>3</sub>	0	S	
10	44	"	"	 -CO-V <sup>0</sup> \	-H	"	"	
15	45	"	"	 -CO-V <sup>0</sup> \	"	"	"	
20	46	"	"	n-C <sub>4</sub> H <sub>9</sub> -CO-V <sup>0</sup> \	"	"	"	
25	47	"	"	 -CO-V <sup>0</sup> \	"	"	"	
30	48	"	"	 -CO-V <sup>0</sup> \	"	"	"	
35	49	"	"	 -CO-V <sup>0</sup> \	"	"	"	
40	50	"	"	$\text{CH}_3\text{O}-\text{V}^0\backslash$	"	"	"	
45	51	"	"	$\text{C}_6\text{H}_{11}\text{O}-\text{V}^0\backslash$	"	"	"	
50	52	"	"	 -CH <sub>2</sub> O-V <sup>0</sup> \	"	"	"	
55	53	"	"	 -OCO-V <sup>0</sup> \	"	"	"	

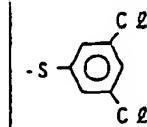
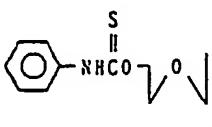
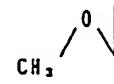
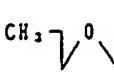
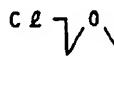
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20	57	"	"		"	"	"	
25	58	"	"		"	"	"	
30	59	"	"		"	"	"	
35	60	"	"		"	"	"	
40	61	"	"		"	"	"	
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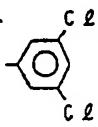
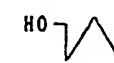
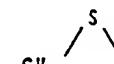
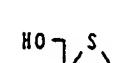
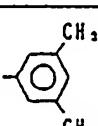
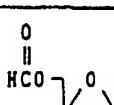
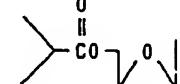
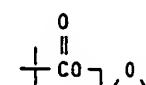
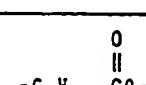
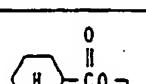
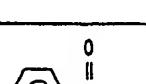
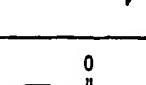
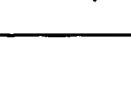
5	65	-CH <sub>3</sub>	-S- 	HO-  S\	-H	O	S	
10	66	"	"	HO-  S\	"	"	O	
15	67	"	-S- 	$\text{HCO}=\text{V}^0\backslash$	"	"	"	
20	68	"	"	$\text{CH}_3\text{CO}=\text{V}^0\backslash$	-CH <sub>2</sub> - 	"	"	
25	69	"	"	$\text{C}(\text{CH}_3)_2\text{CO}=\text{V}^0\backslash$	-H	"	"	
30	70	"	"	$\text{C}_2\text{H}_5\text{CO}=\text{V}^0\backslash$	"	"	"	
35	71	"	"	 -CO-  V <sup>0</sup> \	"	"	"	
40	72	"	"	 -CO-  V <sup>0</sup> \	"	"	"	
45	73	"	"	 -CO-  V <sup>0</sup> \	"	"	"	
50	74	"	"	$\text{CH}_3\text{O}-\text{V}^0\backslash$	"	"	"	
55	75	"	"	$n\text{-C}_5\text{H}_{11}\text{O}-\text{V}^0\backslash$	"	"	"	

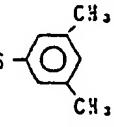
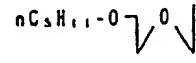
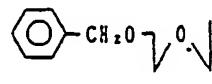
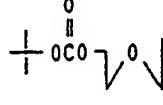
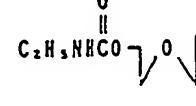
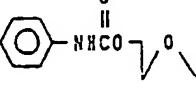
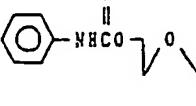
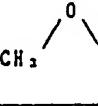
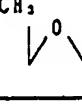
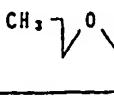
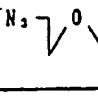
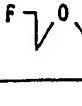
5	76	-CH <sub>3</sub>	-S- 		-H	0	0	
10	77	"	"		"	"	"	
15	78	"	"		"	"	"	
20	79	"	"		"	"	"	
25	80	"	"		"	"	"	
30	81	"	"		"	"	"	
35	82	"	"		"	"	"	
40	83	"	"		"	"	"	
45	84	"	"		"	"	"	
50	85	"	"		"	"	"	
55	86	"	"		"	"	"	

5	87	-CH <sub>3</sub>	-S- 	CH <sub>2</sub> 	-H	0	0	
10	88	"	"	H	"	"	"	
15	89	"	"	CH <sub>3</sub>	"	"	"	
20	90	"	"	CH <sub>3</sub>	"	"	"	
25	91	"	"	CH <sub>3</sub> 	"	"	"	
30	92	"	"	HO 	"	"	"	
35	93	"	"	CH <sub>3</sub> 	"	"	"	
40	94	"	"	HO 	"	"	"	
45	95	"	-S- 	HC=O 	"	"	"	
50	96	"	"	CH <sub>3</sub> 	"	"	"	
55	97	"	"	CH <sub>3</sub> 	"	"	"	

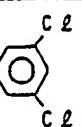
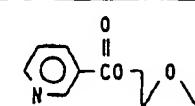
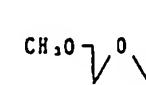
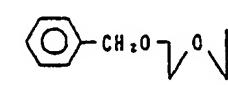
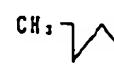
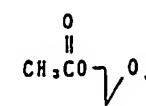
5	98	-CH <sub>3</sub>			-H	0	0	
10	99	"	"		"	"	"	
15	100	"	"		"	"	"	
20	101	"	"		"	"	"	
25	102	"	"		"	"	"	
30	103	"	"		"	"	"	
35	104	"	"		"	"	"	
40	105	"	"		"	"	"	
45	106	"	"		"	"	"	
50	107	"	"		"	"	"	
55	108	"	"		"	"	"	

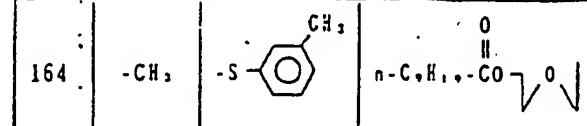
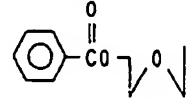
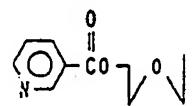
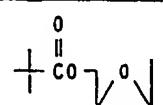
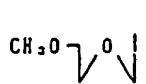
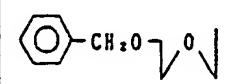
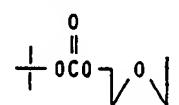
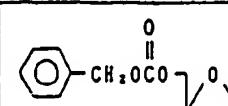
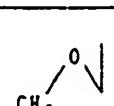
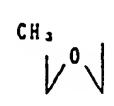
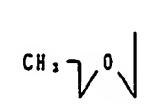
5	109	-CH <sub>3</sub>			-H	0	0	
10	110	"	"		"	"	"	
15	111	"	"		"	"	"	
20	112	"	"		"	"	"	
25	113	"	"		"	"	"	
30	114	"	"		"	"	"	
35	115	"	"		"	"	"	
40	116	"	"		"	"	"	
45	117	"	"		"	"	"	
50	118	"	"		"	"	"	
55	119	"	"		"	"	"	

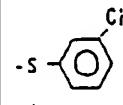
5	120	-CH <sub>3</sub>	-S- 		-H	0	0	
10	121	"	"		"	"	"	
15	122	"	"		"	"	"	
20	123	"	-S- 		"	"	S	
25	124	"	"		"	"	"	
30	125	"	"		"	"	"	
35	126	"	"		"	"	"	
40	127	"	"		"	"	"	
45	128	"	"		"	"	"	
50	129	"	"		"	"	"	
55	130	"	"		"	"	"	

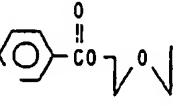
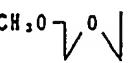
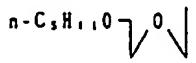
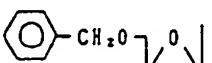
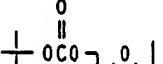
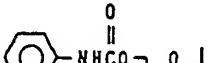
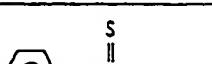
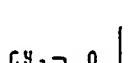
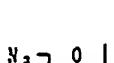
5	131	-CH <sub>3</sub>	-S- 	nC <sub>5</sub> H <sub>11</sub> -O- 	-H	O	S	
10	132	"	"		"	"	"	
15	133	"	"		"	"	"	
20	134	"	"		"	"	"	
25	135	"	"		"	"	"	
30	136	"	"		"	"	"	
35	137	"	"		"	"	"	
40	138	"	"		"	"	"	
45	139	"	"		"	"	"	
50	140	"	"		"	"	"	
55	141	"	"		"	"	"	

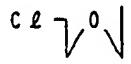
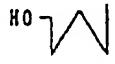
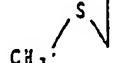
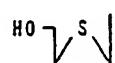
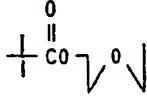
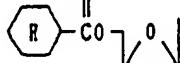
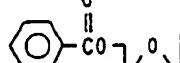
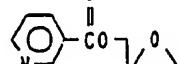
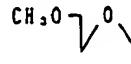
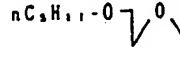
5	142	-CH <sub>3</sub>	<chem>-S-C(=O)c1ccccc1</chem>	<chem>CC(=O)S</chem>	-H	O	S	
10	143	"	"	<chem>H</chem>	"	"	"	
15	144	"	"	<chem>CH3</chem>	"	"	"	
20	145	"	"	<chem>CH3</chem>	"	"	"	
25	146	"	"	<chem>CH3</chem>	"	"	"	
30	147	"	"	<chem>HOCC(=O)S</chem>	"	"	"	
35	148	"	"	<chem>CH3SC(=O)S</chem>	"	"	"	
40	149	"	"	<chem>HOCC(=O)S</chem>	"	"	"	
45	150	"	<chem>-S-C(=O)c1ccccc1</chem>	<chem>CH3C(=O)C(=O)S</chem>	"	"	"	
50	151	"	"	<chem>c1ccccc1C(=O)C(=O)S</chem>	"	"	"	
55	152	"	"	<chem>CC(=O)C(=O)S</chem>	"	"	"	

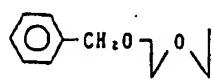
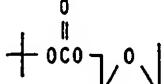
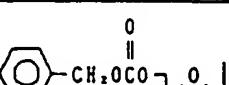
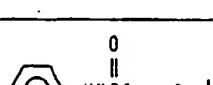
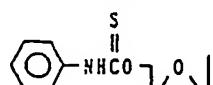
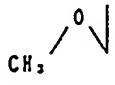
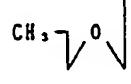
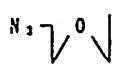
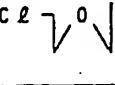
5	153	-CH <sub>3</sub>	-S- 		-H	O	S	
10	154	"	"		"	"	"	
15	155	"	"		"	"	"	
20	156	"	"		"	"	"	
25	157	"	"		"	"	"	
30	158	"	"		"	"	"	
35	159	"	"		"	"	"	
40	160	"	"		"	"	"	
45	161	"	"		"	"	"	
50	162	"	"		"	"	"	
55	163	"	-S- 		"	"	O	

5	164	-CH <sub>3</sub>		-H	0	0	
10	165	"	" 	"	"	"	
15	166	"	" 	"	"	"	
20	167	"	" 	"	"	"	
25	168	"	" 	"	"	"	
30	169	"	" 	"	"	"	
35	170	"	" 	"	"	"	
40	171	"	" 	"	"	"	
45	172	"	" 	"	"	"	
50	173	"	" 	"	"	"	
55	174	"	" 	"	"	"	

5	175	-CH <sub>3</sub>	-S- 	N <sub>3</sub> -V <sup>0</sup> \	-H	0	0	
10	176	"	"	F-V <sup>0</sup> \	"	"	"	
15	177	"	"	C <sub>2</sub> -V <sup>0</sup> \	"	"	"	
20	178	"	"	H	"	"	"	
25	179	"	"	CH <sub>3</sub> -W	"	"	"	
30	180	"	"	HO-W	"	"	"	
35	181	"	"	CH <sub>3</sub> -S\	"	"	"	
40	182	"	"	HO-S\	"	"	"	
45	183	"	-S- 	CH <sub>3</sub> CO-V <sup>0</sup> \	"	"	"	
50	184	"	"	CO-V <sup>0</sup> \	"	"	"	
55	185	"	"	CO-V <sup>0</sup> \	"	"	"	

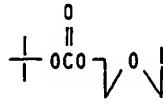
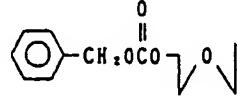
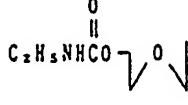
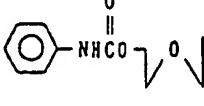
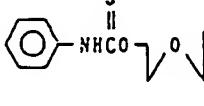
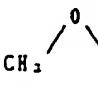
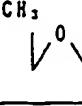
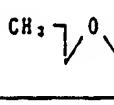
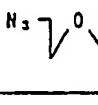
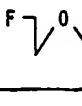
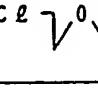
5	186	-CH <sub>3</sub>	-S- 		-H	0	0	
10	187	"	"		"	"	"	
15	188	"	"		"	"	"	
20	189	"	"		"	"	"	
25	190	"	"		"	"	"	
30	191	"	"		"	"	"	
35	192	"	"		"	"	"	
40	193	"	"		"	"	"	
45	194	"	"		"	"	"	
50	195	"	"		"	"	"	
55	196	"	"		"	"	"	

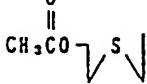
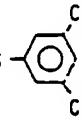
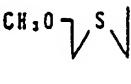
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10	198	"	"		"	"	"	
15	199	"	"		"	"	"	
20	200	"	"		"	"	"	
25	201	"	"		"	"	"	
30	202	"	-CH <sub>2</sub> - 		"	"	"	
35	203	"	"		"	"	"	
40	204	"	"		"	"	"	
45	205	"	"		"	"	"	
50	206	"	"		"	"	"	
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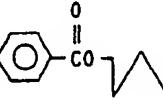
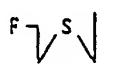
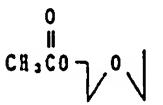
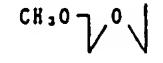
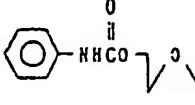
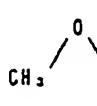
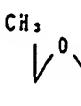
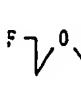
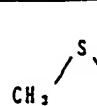
5	208	-CH <sub>3</sub>	-CH <sub>2</sub> - 		-H	0	0	
10	209	"	"		"	"	"	
15	210	"	"		"	"	"	
20	211	"	"		"	"	"	
25	212	"	"		"	"	"	
30	213	"	"		"	"	"	
35	214	"	"		"	"	"	
40	215	"	"		"	"	"	
45	216	"	"		"	"	"	
50	217	"	"		"	"	"	
55	218	"	"		"	"	"	

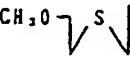
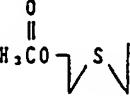
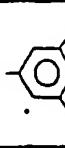
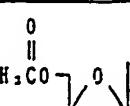
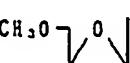
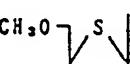
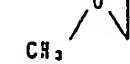
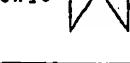
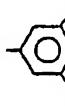
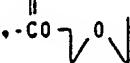
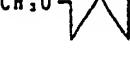
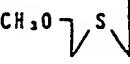
5	219	-CH <sub>3</sub>	-CH <sub>2</sub> - 		-H	0	0	
10	220	"	"		"	"	"	
15	221	"	"		"	"	"	
20	222	"	"		"	"	"	
25	223	"	-S- 		-CH <sub>3</sub>	"	S	
30	224	"	"		-CH <sub>2</sub> - 	"	"	
35	225	"	"		-CH <sub>3</sub>	"	"	
40	226	"	"		"	"	"	
45	227	"	"		"	"	"	
50	228	"	"		"	"	"	
55	229	"	-S- 		"	"	"	

5	230	-CH <sub>3</sub>	<chem>-S-C6H4-CH3</chem>	<chem>CH3O-C(=O)C</chem>	<chem>-CH2-C6H5</chem>	O	S	
10	231	"	"	<chem>N3-C(=O)C</chem>	"	"	"	
15	232	"	"	<chem>F-C(=O)C</chem>	"	"	"	
20	233	"	"	<chem>Cl-C(=O)C</chem>	"	"	"	
25	234	"	"	<chem>CH3O-C(=O)C</chem>	<chem>-CH3</chem>	"	"	
30	235	"	"	<chem>CH3-C(=O)C</chem>	<chem>-CH2-C6H5</chem>	"	"	
35	236	<chem>-C2H5</chem>	<chem>-S-C6H5</chem>	<chem>CH3CO-C(=O)C</chem>	<chem>-H</chem>	"	O	
40	237	"	"	<chem>C6H5-C(=O)C</chem>	"	"	"	
45	238	"	"	<chem>n-C4H9-C(=O)C</chem>	"	"	"	
50	239	"	"	<chem>CH3O-C(=O)C</chem>	"	"	"	
55	240	"	"	<chem>C6H5-CH2O-C(=O)C</chem>	"	"	"	

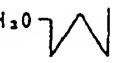
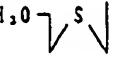
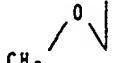
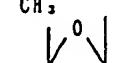
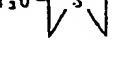
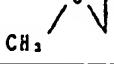
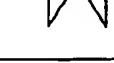
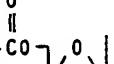
5	241	-C <sub>2</sub> H <sub>5</sub>	-S- 		-H	0	0	
10	242	"	"		"	"	"	
15	243	"	"		"	"	"	
20	244	"	"		"	"	"	
25	245	"	"		"	"	"	
30	246	"	"		"	"	"	
35	247	"	"		"	"	"	123 125
40	248	"	"		"	"	"	
45	249	"	"		"	"	"	
50	250	"	"		"	"	"	
55	251	"	"		"	"	"	

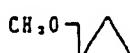
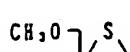
5	252	-C <sub>2</sub> H <sub>5</sub>	-S- 		-H	0	0	107 108
10	253	"	"		"	"	"	
15	254	"	"		"	"	"	
20	255	"	"		"	"	"	
25	256	"	"		-CH <sub>3</sub>	"	"	
30	257	"	"		-CH <sub>2</sub> - 	"	"	
35	258	"	"		-CH <sub>3</sub>	"	"	
40	259	"	"		"	"	"	
45	260	"	-S- 		H	"	S	
50	261	"	"		"	"	O	
55	262	"	"		-CH <sub>3</sub>	"	S	

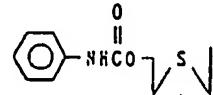
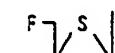
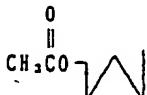
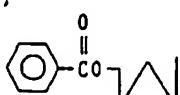
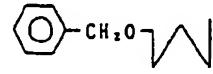
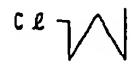
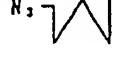
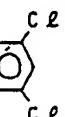
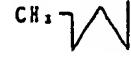
5	263	-C <sub>2</sub> H <sub>5</sub>	-S-C <sub>6</sub> H <sub>4</sub> -C <sub>2</sub>	CH <sub>3</sub> O- 	-H	O	S	
10	264	"	"	CO-C <sub>6</sub> H <sub>4</sub> - 	"	"	"	
15	265	"	"	CH <sub>3</sub> -S- 	-CH <sub>3</sub>	"	"	
20	266	-CH=CHBr	-S-C <sub>6</sub> H <sub>4</sub> -	CH <sub>3</sub> CO- 	H	"	"	
25	267	"	"	CH <sub>3</sub> O- 	"	"	O	
30	268	"	"	CO-NH-C <sub>6</sub> H <sub>4</sub> - 	"	"	"	
35	269	"	"	CH <sub>3</sub> - 	"	"	"	
40	270	"	"	CH <sub>3</sub> - 	"	"	"	1 4 3 1 4 8
45	271	"	"	CH <sub>3</sub> - 	"	"	S	
50	272	"	"	HO- 	"	"	"	
55	273	"	"	CH <sub>3</sub> - 	"	"	"	

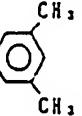
5	274.	-CH=CHBr	-S- 	CH <sub>3</sub> O- 	-H	O	S	
10	275	"	"	CH <sub>3</sub> CO- 	-CH <sub>3</sub>	"	"	
15	276	"	-S- 	CH <sub>3</sub> CO- 	H	"	O	
20	277	"	"	CH <sub>3</sub> O- 	"	"	"	
25	278	-CH <sub>3</sub>	-S- 	CH <sub>3</sub> O- 	"	"	S	
30	279	"	"	CH <sub>3</sub> - 	"	"	O	
35	280	"	"	"	-CH <sub>2</sub> - 	"	S	
40	281	"	"	CH <sub>3</sub> O- 	H	"	"	
45	282	"	-S- 	n-C <sub>6</sub> H <sub>5</sub> -CO- 	"	"	O	
50	283	"	"	CH <sub>3</sub> O- 	"	"	"	
55	284	"	"	CH <sub>3</sub> O- 	"	"	"	

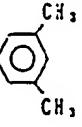
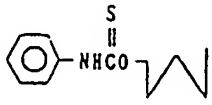
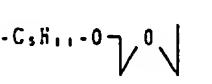
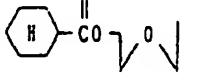
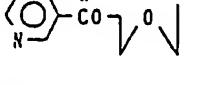
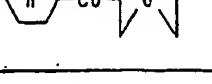
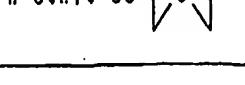
5	285	-CH <sub>3</sub>	<chem>-S-C(=O)c1ccccc1</chem>	<chem>CC(C)OC</chem>	-CH <sub>3</sub>	0	0	
10	286	"	<chem>-S-C(=O)c1cc(Cl)cc(Cl)c1</chem>	<chem>CC(OC)C1=CC(Cl)=CC(Cl)=C1</chem>	H	"	"	
15	287	"	"	<chem>CC(OC)C1=CC=C(S)C=C1</chem>	"	"	"	
20	288	"	<chem>-S-C(=O)c1ccccc1</chem>	<chem>CC(OC)C1=CC=C(Cl)C=C1</chem>	"	"	S	
25	289	"	"	<chem>CC(OC)C1=CC=C(S)C=C1</chem>	"	"	"	
30	290	"	"	<chem>CC(C)OC</chem>	-CH <sub>3</sub>	"	"	
35	291	"	<chem>-S-C(=O)c1cc(Cl)cc(Cl)c1</chem>	<chem>CC(OC)C1=CC(Cl)=CC(Cl)=C1</chem>	H	"	"	
40	292	"	"	<chem>CC(OC)C1=CC=C(Cl)C=C1</chem>	"	"	"	
45	293	"	"	<chem>CC(OC)C1=CC=C(S)C=C1</chem>	"	"	"	
50	294	"	<chem>-S-C(=O)c1ccccc1</chem>	<chem>CC(C)C</chem>	"	"	0	
55	295	"	"	<chem>CC(C)C2CCCCC2</chem>	"	"	"	

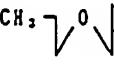
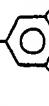
5	296	-CH <sub>3</sub>	-S- 	CH <sub>3</sub> O- 	-H	0	0	
10	297	"	"	CH <sub>3</sub> O- 	"	"	"	
15	298	"	"	CH <sub>3</sub> - 	"	"	S	
20	299	"	"	CH <sub>3</sub> - 	"	"	"	
25	300	"	-S- 	CH <sub>3</sub> O- 	"	"	"	
30	301	"	"	CH <sub>3</sub> O- 	"	"	"	
35	302	"	"	CH <sub>3</sub> - 	"	"	"	
40	303	"	"	CH <sub>3</sub> - 	"	"	"	
45	304	"	-CH <sub>2</sub> - 	n-C <sub>4</sub> H <sub>9</sub> -CO- 	"	"	0	
50	305	"	"	H	"	"	"	
55	306	"	"	CH <sub>3</sub>	"	"	"	

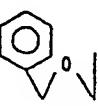
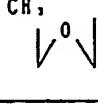
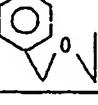
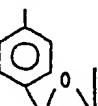
5	307	-CH <sub>3</sub>	-CH <sub>3</sub> - 		-H	0	0	
10	308	"	"	 	"	"	"	
15	309	"	"	 	"	"	"	
20	310	"	"	 	"	"	"	S
25	311	"	"	 	"	"	"	
30	312	"	-S -  	 	"	"	"	
35	313	"	"	  	"	"	"	
40	314	"	"	  	"	"	"	
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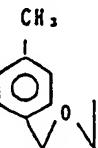
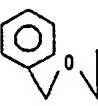
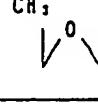
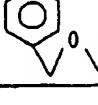
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15	320	"	-S- 		"	"	"	
20	321	"	"		"	"	"	
25	322	"	"		"	"	"	
30	323	"	"		"	"	"	
35	324	"	"		"	"	"	
40	325	"	"		"	"	"	
45	325	"	"		"	"	"	
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55	328	"	-S- 		"	"	O	

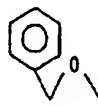
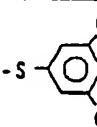
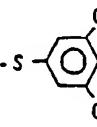
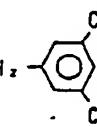
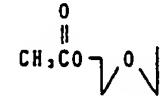
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10	330	"	"	CH <sub>3</sub> CO	"	"	"	
15	331	"	"	n-C <sub>4</sub> H <sub>9</sub> -CO	"	"	"	
20	332	"	"	Ph-CO	"	"	"	
25	333	"	"	Ph-CO	"	"	"	
30	334	"	"	Ph-CO	"	"	"	
35	335	"	"	n-C <sub>5</sub> H <sub>11</sub> -O	"	"	"	
40	336	"	"	CH <sub>3</sub> -CO	"	"	"	
45	337	"	"	Ph-CH <sub>2</sub> CO	"	"	"	
50	338	"	"	CH <sub>3</sub> CH <sub>2</sub> NHCO	"	"	"	
55	339	"	"	Ph-NHCO	"	"	"	

5	340	-CH <sub>3</sub>	-S- 		-H	O	S	
10	341	"	-S- 	n-C <sub>5</sub> H <sub>11</sub> -O- 	"	"	"	
15	342	"	-S- 		"	"	"	
20	343	"	"		"	"	"	
25	344	"	"		"	"	"	
30	345	"	"		"	"	"	
35	346	-C <sub>2</sub> H <sub>5</sub>	-S- 		"	"	"	
40	347	"	"		"	"	"	
45	348	"	"		"	"	"	
50	349	"	"		"	"	"	
55	350	"	"		"	"	"	

5	351	-CH=CHBr	-S- 	I C <sub>2</sub> H <sub>5</sub>	-y	0	S	
10	352	"	"	CH <sub>3</sub> 	"	"	"	
15	353	"	"	 -CO- 	"	"	"	
20	354	"	"	 -CH <sub>2</sub> -CO- 	"	"	"	
25	355	"	"	CH <sub>3</sub> 	"	"	"	
30	356	"	"	HO- 	"	"	"	
35	357	-C <sub>2</sub> H <sub>5</sub>	-S-  CH <sub>3</sub> CH <sub>3</sub>	CH <sub>3</sub> 	"	"	0	165 166
40	358	"	-S- 	"	"	"	S	106 109
45	359	"	-S-  CH <sub>3</sub> CH <sub>3</sub>	"	"	"	"	155 156
50	360	"	-S- 		"	"	0	110 112
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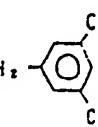
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10	353	-C <sub>2</sub> H <sub>5</sub>	"	"	"	"	151 153	
15	364	"		"	"	"	158 160	
20	365	"			"	"	0	159 162
25	366	"	"	"	"	"	S	112 116
30	367	"	"		"	"	0	
35	368	"	"	"	"	"	S	
40	369	"	-S- 		"	"	0	
45	370	"	-S- 	"	"	"	"	
50	371	"	-S- 	"	"	"	"	
55								

5								
10	372	-C <sub>2</sub> H <sub>5</sub>	-S- 		-H	O	S	157 160
15	373	"	-S- 	"	"	"	"	
20	374	"	-S- 	"	"	"	"	
25	375	"	-S- 		"	"	O	
30	376	"	"	"	"	"	S	
35	377	"	"		"	"	O	
40	378	"	"	"	"	"	S	
45	379	-CH <sub>3</sub>	-S- 		"	"	"	
50	380	"	-S- 	"	"	"	O	
55	381	"	"	"	"	"	S	

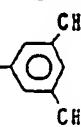
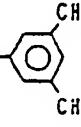
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10	383	"	"	"	"	"	S	
15	384	"	-S- 	"	"	"	0	
20	385	"	"	"	"	"	S	
25	386	"	-S- 	"	"	"	0	
30	387	"	"	"	"	"	S	
35	388	"	-CH <sub>2</sub> - 	"	"	"	0	
40	389	"	"	"	"	"	S	
45	390	"	-CH <sub>2</sub> - 	"	"	"	0	
50	391	"	"	"	"	"	S	
55	392	"	-S- 		"	"	"	

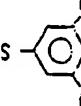
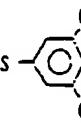
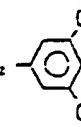
5	393	"	<chem>-S-C(=O)c1ccccc1</chem>	<chem>CH3CO-C(=O)O</chem>	"	"	"	
10	394	"	<chem>-CH2-C(=O)c1ccccc1</chem>	"	"	"	"	
15	395	"	<chem>-CH2-C(=O)c1cc(C)c(cc1)C</chem>	"	"	"	0	
20	396	"	"	"	"	"	S	
25	397	"	<chem>-CH2-C(=O)c1cc(C)c(cc1)C</chem>	<chem>CH3CH2NHCO-C(=O)O</chem>	"	"	"	
30	398	"	"	"	"	"	0	
35	399	"	<chem>-S-C(=O)c1cc(Cl)ccc1</chem>	<chem>CH3-C(=O)O</chem>	"	"	S	
40	400	"	"	<chem>CH3-C(=O)O</chem>	"	"	"	
45	401	"	<chem>-CH2-C(=O)c1cc(C)c(cc1)C</chem>	<chem>CH3-C(=O)O</chem>	"	"	0	
50	402	"	"	"	"	"	S	
55	403	"	"	<chem>CH3-C(=O)O</chem>	"	"	0	

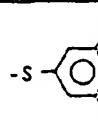
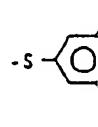
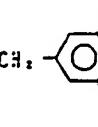
5	404	-CH <sub>3</sub>	<chem>-CH2-c1ccccc1C(C)C</chem>	<chem>CC(=O)C</chem>	-H	O	S	
10	405	"	<chem>-S-c1ccccc1</chem>	<chem>FC(=O)C</chem>	"	"	"	
15	406	"	<chem>-S-c1ccccc1CCl</chem>	"	"	"	"	
20	407	"	<chem>-CH2-c1ccccc1</chem>	"	"	"	"	
25	408	"	<chem>-CH2-c1ccccc1C(C)C</chem>	"	"	"	O	
30	409	"	"	"	"	"	S	
35	410	"	<chem>-S-c1ccccc1</chem>	<chem>CC(=O)C</chem>	"	"	O	
40	411	"	<chem>-S-c1ccccc1C(C)C</chem>	"	"	"	S	
45	412	"	<chem>-CH2-c1ccccc1</chem>	"	"	"	"	
50	413	"	<chem>-CH2-c1ccccc1C(C)C</chem>	"	"	"	O	
55	414	"	"	"	"	"	S	

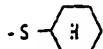
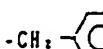
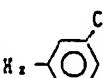
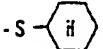
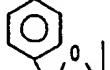
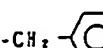
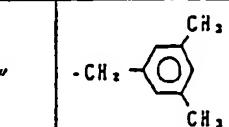
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10	416	"	-S- 	"	"	"	"	
15	417	"	-CH <sub>2</sub> - 	"	"	"	"	
20	418	"	-CH <sub>2</sub> - 	"	"	"	O	
25	419	"	"	"	"	"	S	
30	420	"	-S- 		"	"	O	
35	421	"	"	"	"	"	S	
40	422	-C <sub>2</sub> H <sub>5</sub>	"	"	"	"	O	
45	423	"	"	"	"	"	S	
50	424	-CH <sub>3</sub>	-S- 	"	"	"	O	
55	425	"	"	"	"	"	S	

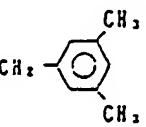
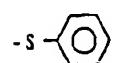
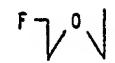
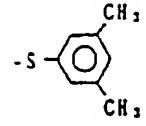
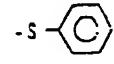
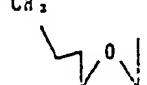
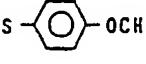
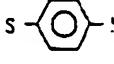
5	426	-C <sub>2</sub> H <sub>5</sub>	<chem>-S-c1ccccc1C</chem>	<chem>CC(=O)S\c1ccccc1</chem>	-H	0	0	
10	427	"	"	"	"	"	S	
15	428	-CH <sub>3</sub>	<chem>-S-c1ccccc1CC</chem>	"	"	"	0	
20	429	"	"	"	"	"	S	
25	430	-C <sub>2</sub> H <sub>5</sub>	"	"	"	"	0	
30	431	"	<chem>-S-c1ccccc1CC</chem>	"	"	"	S	
35	432	-CH <sub>3</sub>	<chem>-S-c1ccccc1C(=O)C</chem>	"	"	"	0	
40	433	"	"	"	"	"	S	
45	434	-C <sub>2</sub> H <sub>5</sub>	"	"	"	"	0	
50	435	"	"	"	"	"	S	
55	436	-CH <sub>3</sub>	<chem>-CH2-c1ccccc1</chem>	"	"	"	0	

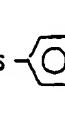
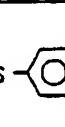
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10	438	-C <sub>2</sub> H <sub>5</sub>	"	"	"	"	O	
15	439	"	"	"	"	"	S	
20	440	-CH <sub>3</sub>	-CH <sub>2</sub> - 	"	"	"	O	
25	441	"	"	"	"	"	S	
30	442	-C <sub>2</sub> H <sub>5</sub>	-CH <sub>2</sub> - 	"	"	"	O	
35	443	"	"	"	"	"	S	
40	444	-CH <sub>3</sub>	-S- 	"	"	"	O	
45	445	"	"	"	"	"	S	
50	446	-C <sub>2</sub> H <sub>5</sub>	"	"	"	"	O	
55	447	"	"	"	"	"	S	

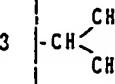
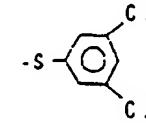
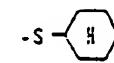
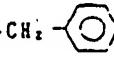
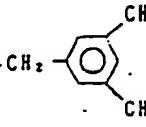
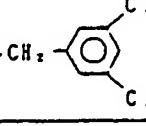
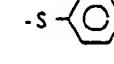
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10	449	"	-S- 	"	"	"	O	
15	450	"	"	"	"	"	S	
20	451	"	-S- 	"	"	"	O	
25	452	"	"	"	"	"	S	
30	453	"	-S- 	"	"	"	O	
35	454	"	"	"	"	"	S	
40	455	"	-CH <sub>2</sub> - 	"	"	"	O	
45	456	"	"	"	"	"	S	
50	457	"	-CH <sub>2</sub> - 	"	"	"	O	
55	458	"	"	"	"	"	S	

5	459	-C <sub>2</sub> H <sub>5</sub>	-S- 		-H	"	S	
10	460	"	-S- 	"	"	"	O	
15	461	"	"	"	"	"	S	
20	462	"	-S- 	"	"	"	O	
25	453	"	"	"	"	"	S	
30	464	"	-S- 	"	"	"	O	
35	465	"	"	"	"	"	S	
40	466	"	-CH <sub>2</sub> - 	"	"	"	O	
45	467	"	"	"	"	"	S	
50	468	"	-CH <sub>2</sub> - 	"	"	"	O	
55	469	"	"	"	"	"	S	

5	470	-C <sub>2</sub> H <sub>5</sub>	-S- 		-H	0	0	
10	471	"	"	"	"	"	S	
15	472	"	-CH <sub>2</sub> - 	"	"	"	0	92.5 95
20	473	"	"	"	"	"	S	
25	474	"	-CH <sub>2</sub> - 	"	"	"	0	160 160.7
30	475	"	"	"	"	"	S	
35	476	"	-S- 		"	"	0	
40	477	"	"	"	"	"	S	
45	478	"	-CH <sub>2</sub> - 	"	"	"	0	
50	479	"	"	"	"	"	S	
55	480	"	-CH <sub>2</sub> - 	"	"	"	0	

5	481	-C <sub>2</sub> H <sub>5</sub>	-CH <sub>2</sub> - 		-H	O	S	
10	482	"	-S- 		"	"	"	
15	483	"	-S- 	"	"	"	0	
20	484	"	"	"	"	"	S	
25	485	-CH <sub>3</sub>	-S- 		"	"	0	118 120
30	485	"	-S- 		"	"	0	
35	487	"	"	"	"	"	S	
40	488	-C <sub>2</sub> H <sub>5</sub>	"	"	"	"	0	
45	489	"	"	"	"	"	S	
50	490	-CH <sub>3</sub>	-S- 	"	"	"	0	
55	491	"	"	"	"	"	S	

5	492	-C <sub>2</sub> H <sub>5</sub>	-S-  -NO <sub>2</sub>	CH <sub>3</sub>   V O V	-H	0	0	
10	493	"	"	"	"	"	S	
15	494	-CH <sub>2</sub> CH <sub>3</sub>	-S- 	CH <sub>3</sub> CO   V O V	"	"	0	
20	495	"	"	CH <sub>3</sub> O   V O V	"	"	"	
25	496	"	"	CH <sub>3</sub>   V O V	"	"	"	112 114
30	497	"	"	"	"	"	S	138 140
35	498	"	-S-  -CH <sub>3</sub>	"	"	"	0	
40	499	"	"	"	"	"	S	
45	500	"	-S-  -CH <sub>3</sub>	"	"	"	0	
50	501	-CH <sub>2</sub> CH <sub>3</sub>	"	CH <sub>3</sub>   V O V	"	"	S	
55	502	"	-S-  -C <sub>2</sub> H <sub>5</sub>	"	"	"	0	

5	503				-H	O	S	
10	504	"		"	"	"	O	
15	505	"	"	"	"	"	S	
20	506	"		"	"	"	O	
25	507	"	"	"	"	"	S	
30	508	"		"	"	"	O	
35	509	"	"	"	"	"	S	
40	510	"		"	"	"	O	
45	511	"	"	"	"	"	S	
50	512	"			"	"	138 141	
55	513	"	"	"	"	"	S	165 168

5	S14	<chem>CC(C)C</chem>	<chem>-S-C6(C)C(=O)C6</chem>	<chem>C1=CC=C1OC</chem>	-8	0	0	
10	S15	-	-	-	-	-	S	
15	S16	-	<chem>-S-C6(C)C(=O)C6</chem>	-	-	-	0	
20	S17	-	-	-	-	-	S	
25	S18	-	<chem>-S-C6H6</chem>	-	-	-	0	
30	S19	-	-	-	-	-	S	
35	S20	-	<chem>-CH2-C6H6</chem>	-	-	-	0	
40	S21	-	-	-	-	-	S	
45	S22	-	<chem>-CH2-C6(C)C(=O)C6</chem>	-	-	-	0	
50	S23	-	-	-	-	-	S	
55	S24	-	<chem>-CH2-C6(C)C(=O)C6</chem>	-	-	-	0	

5	525				-H	O	S	
10	526	-			-	-	O	
15	527	-	-	-	-	-	S	
20	528	-		-	-	-	O	
25	529	-	-	-	-	-	S	
30	530	-		-	-	-	O	
35	531	-	-	-	-	-	S	
40	532	-		-	-	-	O	
45	533	-	-	-	-	-	S	
50	534	-		-	-	-	O	
55	535	-	-	-	-	-	S	

5	536	$-\text{CH}(\text{CH}_3)_2$	$-\text{CH}_2-\text{C}_6\text{H}_4-$	$\text{F}-\text{V}^0\text{V}$	-H	0	0	
10	537	-	-	-	-	-	S	
15	538	-	$-\text{CH}_2-\text{C}_6\text{H}_3(\text{CH}_3)_2-$	-	-	-	0	
20	539	-	-	-	-	-	S	
25	540	-	$-\text{CH}_2-\text{C}_6\text{H}_3(\text{Cl})_2-$	-	-	-	0	
30	541	-	-	-	-	-	S	
35	542	-	$-\text{S}-\text{C}_6\text{H}_4-$	$\text{CH}_3-\text{V}$	-	-	0	
40	543	-	-	-	-	-	S	
45	544	-	$-\text{S}-\text{C}_6\text{H}_3(\text{CH}_3)_2-$	-	-	-	0	
50	545	-	-	-	-	-	S	
55	546	-	$-\text{S}-\text{C}_6\text{H}_3(\text{Cl})_2-$	-	-	-	0	

5	547	$\text{CH}_3$ $\text{CH}_3$	$-\text{S}-\text{C}_6\text{H}_4-\text{C}_6\text{H}_4-\text{S}-$	$\text{CH}_3$ 	-B	O	S	
10	548	-	$-\text{S}-\text{C}_6\text{H}_4-\text{H}-$	-	-	-	O	
15	549	-	-	-	-	-	S	
20	550	-	$-\text{CH}_2-\text{C}_6\text{H}_4-$	-	-	-	O	
25	551	-	-	-	-	-	S	
30	552	-	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_3$	-	-	-	O	
35	553	-	-	-	-	-	S	
40	554	-	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{C}_6\text{H}_4-\text{S}-$	-	-	-	O	
45	555	-	-	-	-	-	S	
50	556	-	$-\text{S}-\text{C}_6\text{H}_4-$	$\text{CH}_3$ 	-	-	O	
55	557	-	-	-	-	-	S	

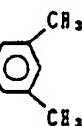
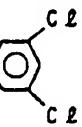
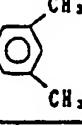
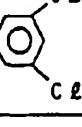
5	558				-B	0	0	
10	559	-	-	-	-	-	S	
15	560	-		-	-	-	0	
20	561	-	-	-	-	-	S	
25	562	-		-	-	-	0	
30	563	-	-	-	-	-	S	
35	564	-		-	-	-	0	
40	565	-	-	-	-	-	S	
45	566	-		-	-	-	0	
50	567	-	-	-	-	-	S	
55	568	-		-	-	-	0	

5	569				-H	O	S	
10	570				-	-	O	
15	571	-		-	-	-	S	
20	572	-	-		-	-	O	
25	573	-	-	-	-	-	S	
30	574	-			-	-	O	94 97
35	575	-	-	-	-	-	S	123 124
40	576	-		-	-	-	O	
45	577	-	-	-	-	-	S	
50	578	-		-	-	-	O	
55	579	-	-	-	-	-	S	

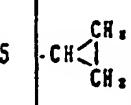
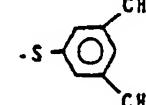
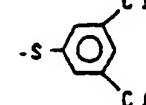
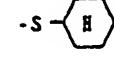
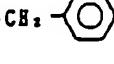
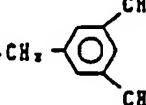
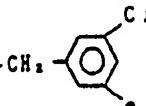
5	580	<chem>C#C1CC1</chem>	<chem>S-c1ccc(cc1)C#C</chem>	<chem>CC(=O)OC</chem>	-H	0	0
10	581	-	-	-	-	-	S
15	582	-	<chem>-Sc1ccccc1</chem>	-	-	-	0
20	583	-	-	-	-	-	S
25	584	-	<chem>-C#Cc1ccccc1</chem>	-	-	-	0
30	585	-	-	-	-	-	S
35	586	-	<chem>-C#Cc1ccc(cc1)C#C</chem>	-	-	-	0
40	587	-	-	-	-	-	S
45	588	-	<chem>-C#Cc1ccc(cc1)C#C</chem>	-	-	-	0
50	589	-	-	"	-	-	S
55	590	-	<chem>-Sc1ccccc1</chem>	<chem>CC1=CC=C1OC</chem>	-	-	0

5	591				-H	O	S	
10	592	-		-	-	-	O	
15	593	-	-	-	-	-	S	
20	594	-		-	-	-	O	
25	595	-	-	-	-	-	S	
30	596	-		-	-	-	O	
35	597	-	-	-	-	-	S	
40	598	-		-	-	-	O	
45	599	-	-	-	-	-	S	
50	600	-		-	-	-	O	
55	601	-	-	-	-	-	S	

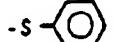
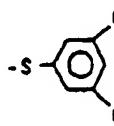
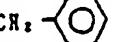
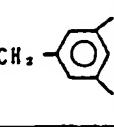
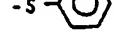
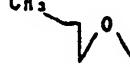
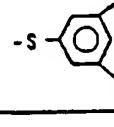
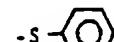
5	602				-S	0	0	
10	603	-	-	-	-	-	S	
15	604	-			-	-	0	
20	605	-	-	-	-	-	S	
25	606	-		-	-	-	0	
30	607	-	-	-	-	-	S	
35	608	-		-	-	-	0	
40	609	-	-	-	-	-	S	
45	610	-		-	-	-	0	
50	611	-	-	-	-	-	S	
55	612	-		-	-	-	0	

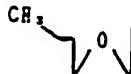
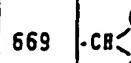
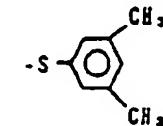
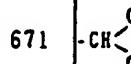
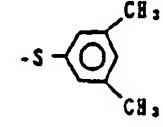
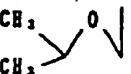
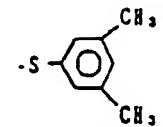
5	613	$\text{CH}_2$ $\text{CH}_2$	$-\text{CH}_2-$ 	$\text{F}-\text{O}-$ 	-H	O	S	
10	614	-	$-\text{CH}_2-$ 	-	-	-	O	
15	615	-	-	-	-	-	S	
20	616	-	$-\text{CH}_2-$ 	-	-	-	O	
25	617	-	-	-	-	-	S	
30	618	-	$-\text{S}-$ 	$\text{CH}_2$ 	-	-	O	
35	619	-	-	-	-	-	S	
40	620	-	$-\text{S}-$ 	-	-	-	O	
45	621	-	-	-	-	-	S	
50	622	-	$-\text{S}-$ 	-	-	-	O	
55	623	-	-	-	-	-	S	

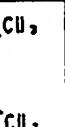
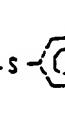
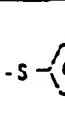
5	624	$-\text{CH}_2-\text{I}$ $\text{CH}_3$	$-\text{S}-\text{C}_6\text{H}_5$	$\text{CH}_3$ 	-R	0	0	
10	625	-	-	-	-	-	S	
15	626	-	$-\text{CH}_2-\text{C}_6\text{H}_5$	-	-	-	0	
20	627	-	-	-	-	-	S	
25	628	-	$-\text{CH}_2-\text{C}_6\text{H}_3(\text{CH}_3)_2$	-	-	-	0	
30	629	-	-	-	-	-	S	
35	630	-	$-\text{CH}_2-\text{C}_6\text{H}_3(\text{Cl})_2$	-	-	-	0	
40	631	-	-	-	-	-	S	
45	632	-	$-\text{S}-\text{C}_6\text{H}_5$	$\text{CH}_3$ 	-	-	0	
50	633	-	-	-	-	-	S	
55	634	-	$-\text{S}-\text{C}_6\text{H}_3(\text{CH}_3)_2$	-	-	-	0	

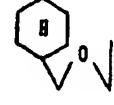
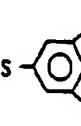
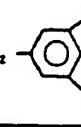
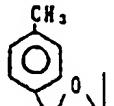
5	635				-H	O	S	
10	636	-		-	-	-	O	
15	637	-	-	-	-	-	S	
20	638	-		-	-	-	O	
25	639	-	-	-	-	-	S	
30	640	-		-	-	-	O	
35	641	-	-	-	-	-	S	
40	642	-		-	-	-	O	
45	643	-	-	-	-	-	S	
50	644	-		-	-	-	O	
55	645	-	-	-	-	-	S	

5	646	$\alpha\text{-C}_3\text{H}_5$	<chem>-S-c1ccccc1</chem>	<chem>CC(=O)OCC</chem>	-H	0	0	
10	647	-	<chem>-S-c1cc(C)c(C)cc1</chem>	<chem>CC(=O)OCC</chem>	-	-	S	
15	648	-	<chem>-S-c1ccccc1</chem>	<chem>CCOC</chem>	-	-	0	
20	649	-	-	-	-	-	S	
25	650	-	<chem>-S-c1cc(C)c(C)cc1</chem>	-	-	-	0	
30	651	-	-	-	-	-	S	
35	652	-	<chem>-CH2-c1ccccc1</chem>	-	-	-	0	
40	653	-	-	-	-	-	S	
45	654	-	<chem>-CH2-c1cc(C)c(C)cc1</chem>	-	-	-	0	
50	655	-	-	-	-	-	S	
55	656	-	<chem>-S-c1ccccc1</chem>	<chem>c1ccccc1OC</chem>	-	-	0	

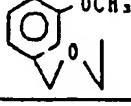
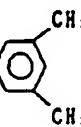
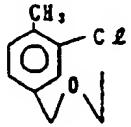
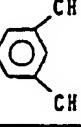
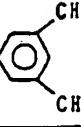
6	657	n-C <sub>5</sub> H <sub>11</sub>	-S- 		-R	O	S	
10	658	-	-S- 	-	-	-	O	
15	659	-	-	-	-	-	S	
20	660	-	-CH <sub>2</sub> - 	-	-	-	O	
25	661	-	-	-	-	-	S	
30	662	-	-CH <sub>2</sub> - 	-	-	-	O	
35	663	-	-	-	-	-	S	
40	664	-CH <sub>3</sub>	-S- 		-	-	S	
45	665	-	-S- 	-	-	-	O	
50	666	-	-	-	-	-	S	
55	667	-CH <sub>2</sub> CH <sub>3</sub>	-S- 	-	-	-	O	

5	668	-CH <sub>2</sub> CH <sub>3</sub>	-S- 		-H	O	S	
10	669						O	
15	670						S	
20	671		-S- 				O	
25	672						S	
30	673						O	
35	674						S	
40	675	-C <sub>2</sub> H <sub>5</sub>	-S- 			O	119 121	
45	676						S	141 142
50	677						O	
55	678						S	

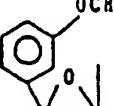
5	679	-C <sub>2</sub> H <sub>5</sub>	-CH <sub>2</sub> - 	-CH <sub>3</sub> CH <sub>3</sub> O ↓	-	0	0	-
10	680	-	-	-	-	-	S	-
15	681	-CH <sub>2</sub> CH <sub>3</sub>	-S- 	-	-	-	0	-
20	682	-	-	-	-	-	S	-
25	683	-	-S- 	-	-	-	0	-
30	684	-	-	-	-	-	S	-
35	685	-C <sub>2</sub> H <sub>5</sub>	-S- 	-C <sub>6</sub> H <sub>5</sub> O ↓	-	-	0	167 171
40	686	-	-	-	-	-	S	139 141
45	687	-CH <sub>2</sub> CH <sub>3</sub>	-S- 	-	-	-	0	-
50	688	-	-	-	-	-	S	-
55	689	-C <sub>2</sub> H <sub>5</sub>	-S- 	-C <sub>6</sub> H <sub>5</sub> O ↓	-	-	0	115 116

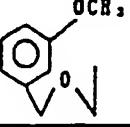
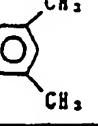
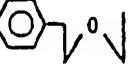
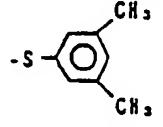
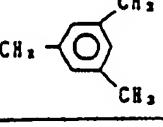
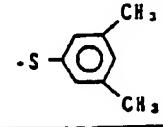
5	690	-C <sub>2</sub> H <sub>5</sub>	-S- 		-H	O	S	134 135
10	691	-	-S- 	-	-	-	O	-
15	692	-	-	-	-	-	S	-
20	693	-	-CH <sub>2</sub> - 	-	-	-	O	-
25	694	-	-	-	-	-	S	-
30	695	-	-CH <sub>2</sub> - 	-	-	-	O	-
35	696	-	-	-	-	-	S	-
40	697	-CH <sub>2</sub> CH <sub>3</sub>	-S- 	-	-	-	O	-
45	698	-	-	-	-	-	S	-
50	699	-C <sub>2</sub> H <sub>5</sub>	-CH <sub>2</sub> - 		-	-	O	-
55	700	-	-	-	-	-	S	-

5	701	-C <sub>6</sub> H <sub>5</sub>	-CH <sub>2</sub> -		-H	0	0	
10	702	-	-	-	-	-	S	
15	703	-	-S-		-	-	0	
20	704	-	-	-	-	-	S	132 134
25	705	-	-S-	-	-	-	0	
30	706	-	-	-	-	-	S	
35	707	-	-CH <sub>2</sub> -	-	-	-	0	
40	708	-	-S-		-	-	0	
45	709	-	-	-	-	-	S	
50	710	-	-S-	-	-	-	0	
55	711	-	-	-	-	-	S	

5	712	-C <sub>2</sub> H <sub>5</sub>	-CH <sub>2</sub> - 		-H	0	0	
10	713	-	-	-	-	-	S	
15	714	-	-CH <sub>2</sub> - 	-	-	-	0	
20	715	-	-	-	-	-	S	
25	716	-	-S- 		-	-	0	
30	717	-	-	-	-	-	S	
35	718	-	-S- 	-	-	-	0	
40	719	-	-	-	-	-	S	
45	720	-	-CH <sub>2</sub> - 	-	-	-	0	
50	721	-	-	-	-	-	S	
55	722	-	-CH <sub>2</sub> - 	-	-	-	0	

5	723	-C <sub>2</sub> H <sub>5</sub>	-CH <sub>2</sub> -		-H	0	S	
10	724	-CH <sub>2</sub>	-S-		-	-	0	
15	725	-	-	-	-	-	S	
20	726	-	-S-	-	-	-	0	
25	727	-	-	-	-	-	S	
30	728	-	-CH <sub>2</sub> -	-	-	-	0	
35	729	-	-	-	-	-	S	
40	730	-CH <sub>2</sub>	-CH <sub>2</sub> -	-	-	-	0	
45	731	-	-	-	-	-	S	
50	732	-	-S-		-	-	0	
55	733	-	-	-	-	-	S	

5	734	$-\text{CH}(\text{CH}_3)_2$	$-\text{S}-\text{C}_6\text{H}_3(\text{CH}_3)_2$		-B	0	0	
10	735	-	-	-	-	-	S	
15	736	-	$-\text{CH}_2-\text{C}_6\text{H}_4$	-	-	-	0	
20	737	-	-	-	-	-	S	
25	738	-	$-\text{CH}_2-\text{C}_6\text{H}_3(\text{CH}_3)_2$	-	-	-	0	
30	739	-	-	-	-	-	S	
35	740	-	$-\text{S}-\text{C}_6\text{H}_4$		-	-	0	
40	741	-	-	-	-	-	S	
45	742	-	$-\text{S}-\text{C}_6\text{H}_3(\text{CH}_3)_2$	-	-	-	0	
50	743	-	-	-	-	-	S	
55	744	-	$-\text{CH}_2-\text{C}_6\text{H}_4$	-	-	-	0	

5	745	$\begin{array}{c} \text{CH}_3 \\   \\ -\text{CH}-\text{CH}_3 \end{array}$	$-\text{CH}_2-\text{C}_6\text{H}_4-$		-8	0	S	
10	746	-	$-\text{CH}_2-\text{C}_6\text{H}_4-$		-	-	0	
15	747	-	-	-	-	-	S	
20	748	$-\text{C}_2\text{H}_5$	$-\text{S}-\text{C}_6\text{H}_4-$		-	-	0	108 110
25	749	-	-	-	-	-	S	136 138
30	750	-	-	$\begin{array}{c} \text{CH}_3 \\   \\ \text{C}_3\text{H}_8 \end{array}$	-	-	S	
35	751	-	$-\text{S}-\text{C}_6\text{H}_4-$		-	-	0	
40	752	-	$-\text{CH}_2-\text{C}_6\text{H}_4-$	-	-	-	0	
45	753	-	$-\text{CH}_2-\text{C}_6\text{H}_4-$		-	-	S	
50	754	$\begin{array}{c} \text{CH}_3 \\   \\ -\text{CH}-\text{CH}_3 \end{array}$	$-\text{S}-\text{C}_6\text{H}_4-$	-	-	-	0	
55	755	-	$-\text{S}-\text{C}_6\text{H}_4-$		-	-	S	

5	756				-8	0	0	
10	757	"		"	"	"	S	

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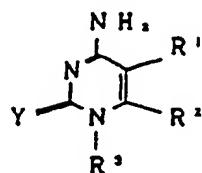
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Table - 2



Compound No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Y	Melting point (°C)
758	-CH <sub>3</sub>	-S-	CH <sub>3</sub> O V	O	
759	-	-	-	S	
760	-C <sub>2</sub> H <sub>5</sub>	-	-	O	
761	-	-	-	S	
762	-CH <sub>3</sub>	-S-	-	O	
763	-	-	-	S	
764	-C <sub>2</sub> H <sub>5</sub>	-	-	O	
764	-	-	-	S	
766	-CH <sub>3</sub>	-S-	-	O	

5	767	-CH <sub>3</sub>	-S-C <sub>6</sub> H <sub>4</sub> -C <sub>6</sub> H <sub>4</sub> -	CH <sub>3</sub> / O \	S	
10	768	-C <sub>2</sub> H <sub>5</sub>	-	-	O	
15	769	-	-	-	S	
20	770	-CH <sub>2</sub> -CH <sub>3</sub>	-S-C <sub>6</sub> H <sub>4</sub> -	-	O	
25	771	-	-	-	S	
30	772	-	-S-C <sub>6</sub> H <sub>4</sub> -CH <sub>3</sub>	-	O	
35	773	-	-	-	S	
40	774	-	-S-C <sub>6</sub> H <sub>4</sub> -C <sub>6</sub> H <sub>4</sub> -	-	O	
45	775	-	-	-	S	
50	776	-	-CH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub> -	-	O	
55	777	-	-	-	S	

5	778				0	
10	779	-	-	-	S	
15	780				0	
20	781	-	-	-	S	
25	782	-		-	0	
30	783	-	-	-	S	
35	784	-		-	0	
40	785	-	-	-	S	
45	786	-		-	0	
50	787	-	-	-	S	
55	788			-	0	

5	789				S	
10	790	-		-	O	
15	791	-	-	-	S	
20	792	-		-	O	
25	793	-	-	-	S	
30	794	-		-	O	
35	795	-	-	-	S	
40	796			-	O	
45	797	-	-	-	S	
50	798	-		-	O	
55	799	-	-	-	S	

5	800				0	
10	801	-	-	-	S	
15	802	-		-	0	
20	803	-	-	-	S	

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The compounds according to the invention of the formula I wherein R<sup>3</sup> represents methyl or branched alkyl or -CH<sub>2</sub>-Z(CH<sub>2</sub>)<sub>n</sub>-R<sup>5</sup> group where R<sup>5</sup> represents a hydrogen, halogen atom, azido, alkoxy, aralkyloxy, optionally substituted aryl group or the like may be prepared in accordance with the following reaction formula (1), (2) or (3):

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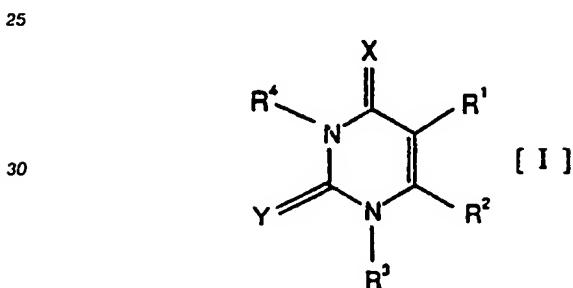
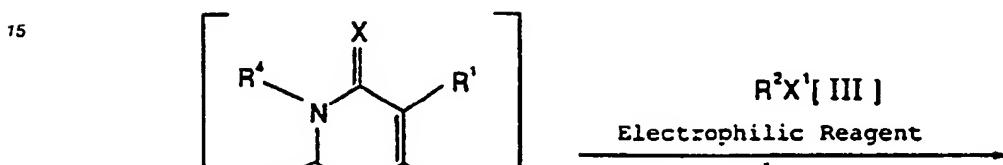
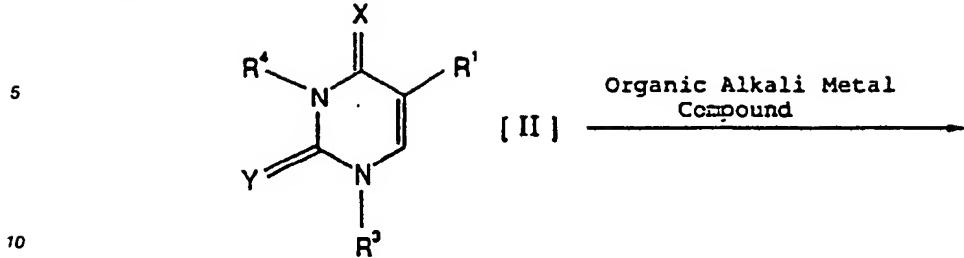
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(1)



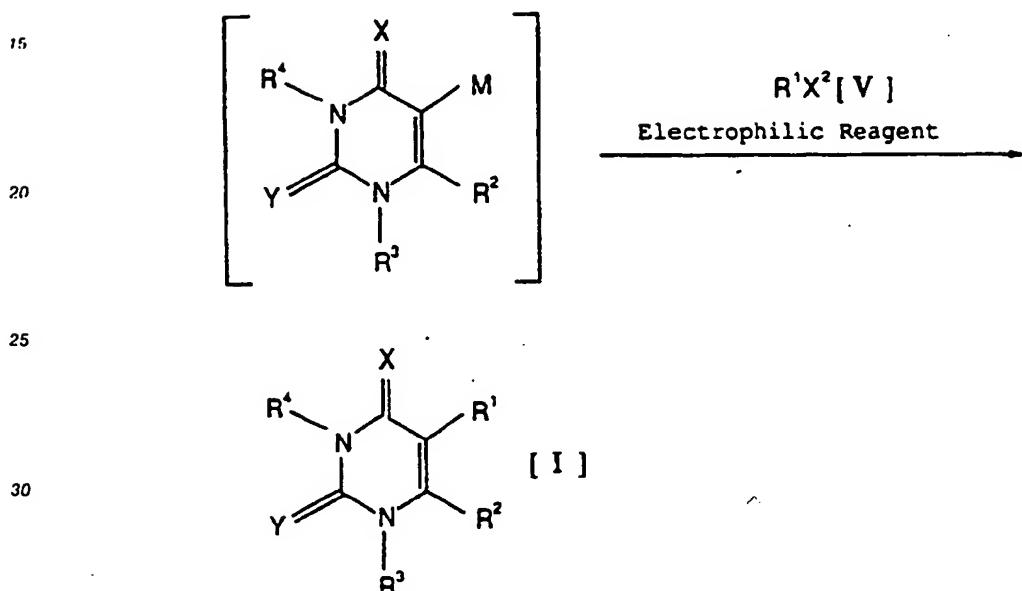
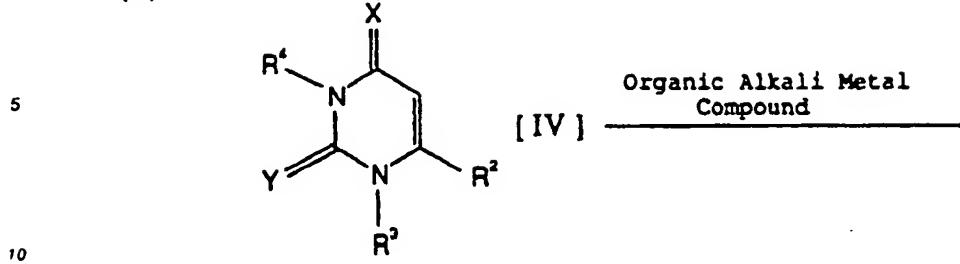
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(2)



35 wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings defined hereinbefore, X<sup>1</sup> and X<sup>2</sup> represent a halogen atom, arylthio, alkoxy group or the like, and M represents an alkaline metal.

40 Firstly, the compound of the formula II or IV is treated with an organic alkali metal compound in an ether solvent such as diethyl ether and tetrahydrofuran at a temperature of -80 to -10 °C for 0.2 to 10 hours.

45 Examples of the organic alkali metal compound include potassium bistrimethylsilylamide, sodium bistrimethylsilylamide and lithium alkylamide, and particularly preferred compounds among those are lithium diisopropylamide (LDA) and lithium 2,2,6,6-tetramethylpiperide (LTMP). Such lithium alkylamides are preferably prepared immediately before the reaction. For example, lithium dialkylamide may be prepared by reacting a secondary amine such as diisopropylamine with an alkyl lithium such as n-butyl lithium in a solvent such as diethyl ether, dioxane, tetrahydrofuran and dimethoxyethane with stirring under the atmosphere of an inert gas such as argon at -80 °C to -10 °C for 0.2 to 5 hours.

50 The organic alkali metal compound is usually used in an amount of 1 to 5 moles per mole of the compound of the general formula II or IV.

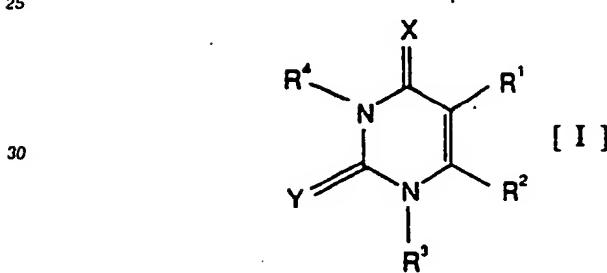
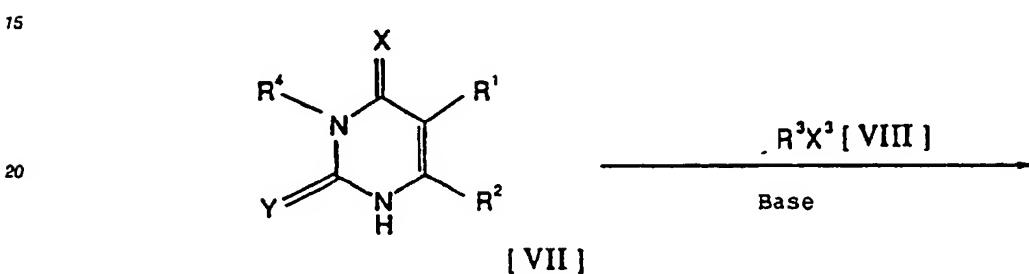
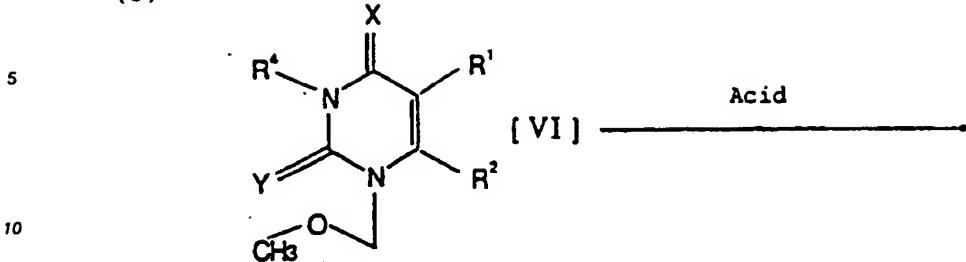
55 Then, the electrophilic reagent of the general formula R<sup>2</sup>X<sup>1</sup> or R<sup>1</sup>X<sup>2</sup> is added to the reaction mixture in a ratio of about 1 to 5 moles to the compound of the general formula II or IV to allow the reaction under the same condition as in the reaction with the organic alkali metal compound.

60 The electrophilic reagent should have a group of R<sup>1</sup> or R<sup>2</sup> defined above, and examples of this reagent includes various diaryl disulfides, arylsulfenyl chlorides, dialkyl disulfides, dicycloalkyl disulfides, alkyl halides, aralkyl halides such as benzyl bromide, acid halides such as benzoyl halide and isobutyric halide, acid anhydrides and esters thereof, arylcarbonylalkyl halides such as phenacyl chloride and the like.

65 The compounds of the general formula II can be prepared by a conventional method.

70 The compounds of the general formula IV can be prepared in accordance with the reaction formula (1) above (R<sup>1</sup> = H).

(3)



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings defined hereinbefore and X<sup>3</sup> represents a halogen atom such as chlorine, bromine and iodine or sulfonyloxy group such as toluenesulfonyloxy and mesyloxy groups.

40 The compounds of the general formula VI are treated with an acid such as hydrochloric acid and bromic acid in a suitable solvent, for example, an alcohol such as methanol and ethanol and water at an appropriate temperature of from room temperature to 100 °C to obtain the compounds of the general formula VII.

45 Then, the compounds of the general formula VII are reacted with the compounds of the general formula VIII in a suitable solvent such as dimethylformamide, dimethyl sulfoxide, acetonitrile and tetrahydrofuran in the presence of a suitable base such as sodium hydride, sodium alkoxide, potassium alkoxide, potassium carbonate and sodium carbonate at a temperature of from ambient temperature to the boiling point of the solvent to obtain the compounds of the general formula I.

50 The starting compounds represented by the general formula VI can be prepared in accordance with the reaction formula (1) or (2).

55 When the objective compound has a hydroxyl group of R<sup>5</sup> or when any intermediate compound of the reactions has a hydroxyl group, the reactions of (1) and (2) should be carried out by using a starting compound or intermediate compound of which hydroxyl group is protected by an appropriate protective group instead of the unprotected compound of the formula II or IV or the like, and the protective group is then eliminated to obtain the target compound.

55 Any protective groups conventionally used for the protection of hydroxyl group may be used for this purpose so long as it is not eliminated under the alkaline condition.

Examples of such protective groups are aralkyl groups such as benzyl, trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, silyl groups such as trimethylsilyl, triethylsilyl, t-butyldimethylsilyl and t-

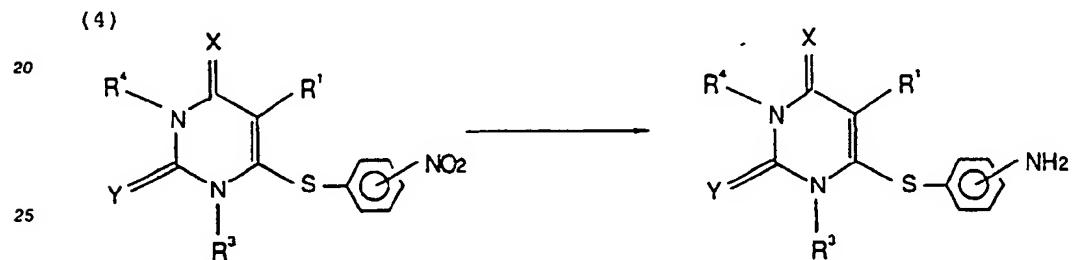
butyldiphenylsilyl, tetrahydropyranyl group and substituted alkyl groups such as methoxymethyl group. Among those protective groups, silyl groups are particularly preferred.

The introduction of the protective group can be carried out by a conventional method.

For example, the introduction of the protective silyl group may be carried out by reacting the compound having the hydroxyl group with 1 to 10 times by mole of silylating reagent such as trimethylsilyl chloride and *t*-butyldimethylsilyl chloride at a temperature of from 0 to 50 °C in the presence of a base such as pyridine, picoline, diethylaniline, dimethylaniline, triethylamine and imidazole in a solvent such as dimethylformamide, acetonitrile, tetrahydrofuran and a mixture of those solvents in any combination.

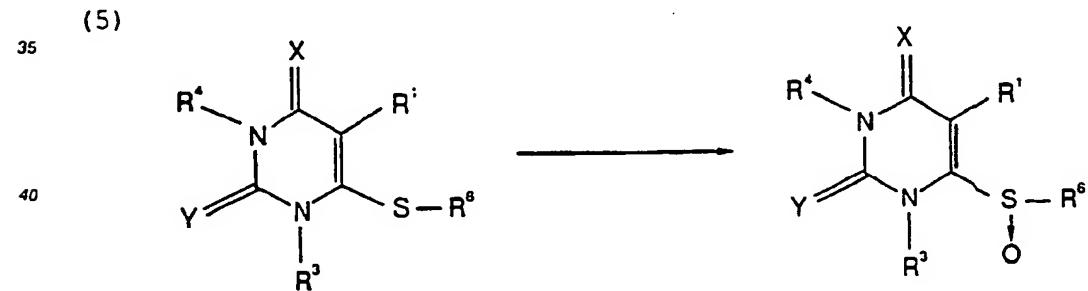
The elimination of the protective group may be carried out by a conventional method corresponding to the kind of the protective group, for example, acid hydrolysis, ammonium fluoride treatment or catalytic reduction.

The compounds obtained by the reactions (1), (2) or (3) which have a nitro substituted phenylthio group at the 6-position may be converted into the compounds having an amino group by hydrogenation in accordance with the reaction formula (4) below. The hydrogenation can be carried out in an organic solvent such as alcohol and acetic acid in the presence of a catalyst such as palladium/carbon at an appropriate temperature of from room temperature to 80 °C:



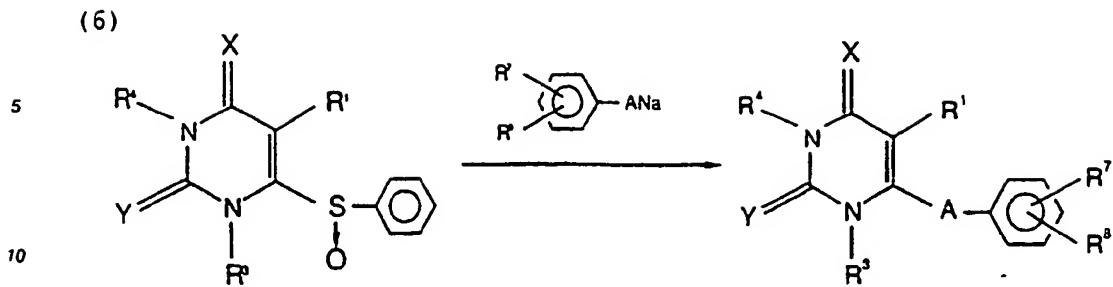
wherein the symbols have the same meanings as defined above.

30 The compounds having an arylthio, alkylthio or cycloalkylthio group can be converted to corresponding compounds having an arylsulfinyl, alkylsulfinyl or cycloalkylsulfinyl group by using an oxidizing agent such as hydrogen peroxide and *m*-chloroperbenzoic acid in accordance with the reaction formula (5) below:



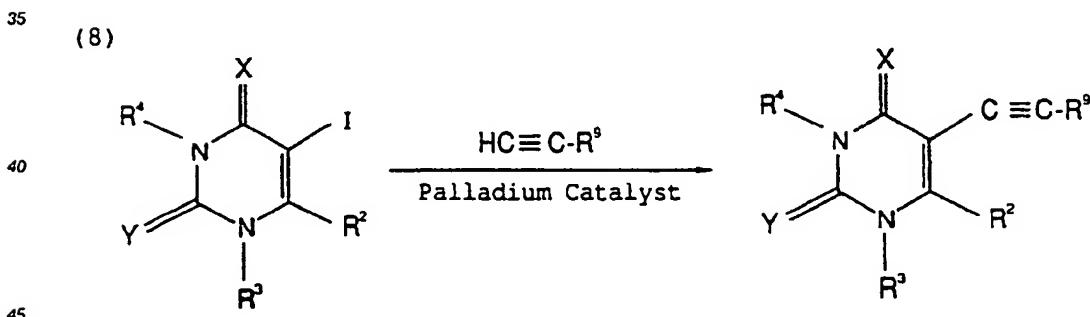
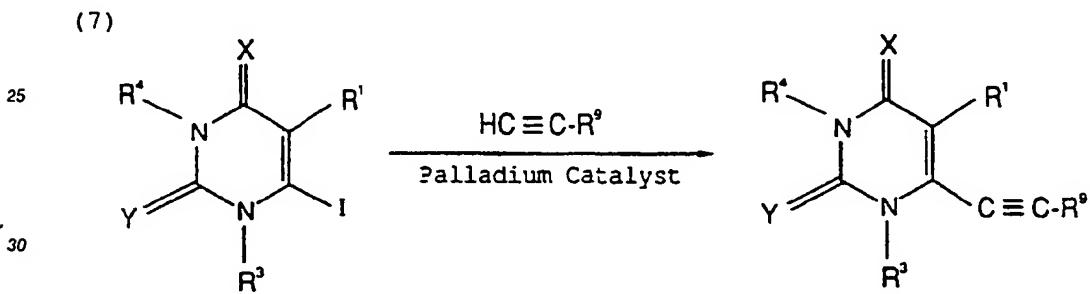
45 wherein R<sup>6</sup> represents an aryl, alkyl or cycloalkyl group and the other symbols have the same meanings as defined above.

50 The compounds having phenyl sulfoxide group can be converted into corresponding compounds having a substituted arylthio or aryloxy group by reacting with sodium arylthiolate or sodium aryloxide having various substituents on the benzene ring in an organic solvent such as tetrahydrofuran, alcohol, dimethylformamide and acetonitrile at an appropriate temperature of from room temperature to 100 °C in accordance with the reaction formula (6) below:



wherein A represents a sulfur or oxygen atom, R<sup>7</sup> and R<sup>8</sup> independently represent a halogen atom such as chlorine, bromine, fluorine and iodine, alkyl group such as methyl, ethyl, propyl and butyl, halogenated alkyl group such as trichloromethyl, alkoxy group such as methoxy, ethoxy, propoxy and butoxy, hydroxyl group, nitro group, amino group, cyano group and acyl group such as acetyl, and the other symbols have the same meanings as defined above.

The present compounds may be also prepared in accordance with, for example, the reaction formula (7) or (8) below:

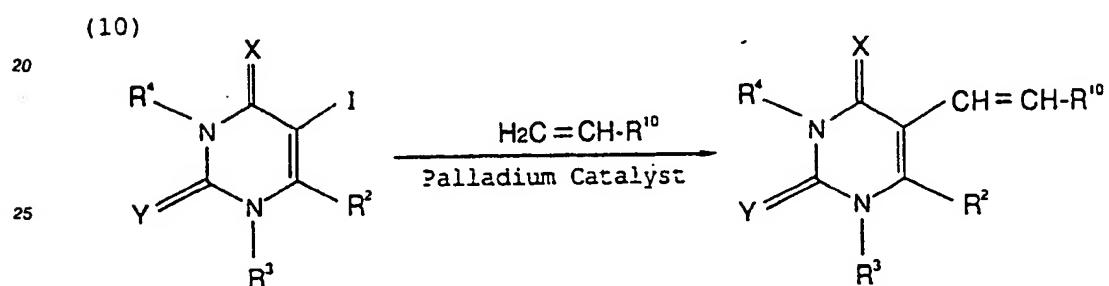
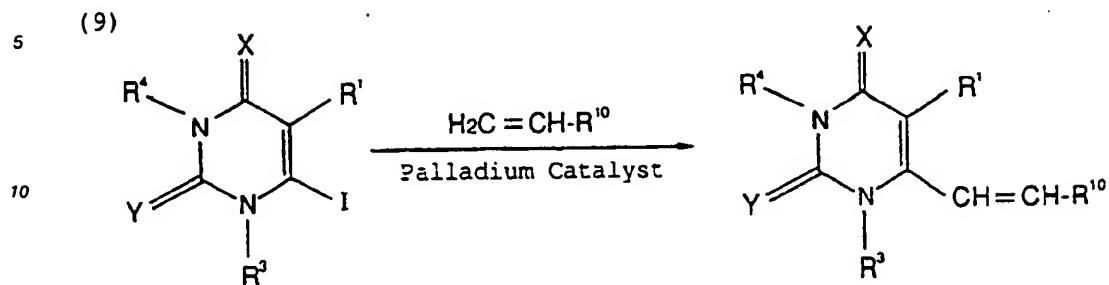


wherein R<sup>9</sup> represents an alkyl group such as methyl and ethyl, aryl group such as phenyl and toluyl, a protective group such as silyl group or the like, and the other symbols have the same meanings as defined above.

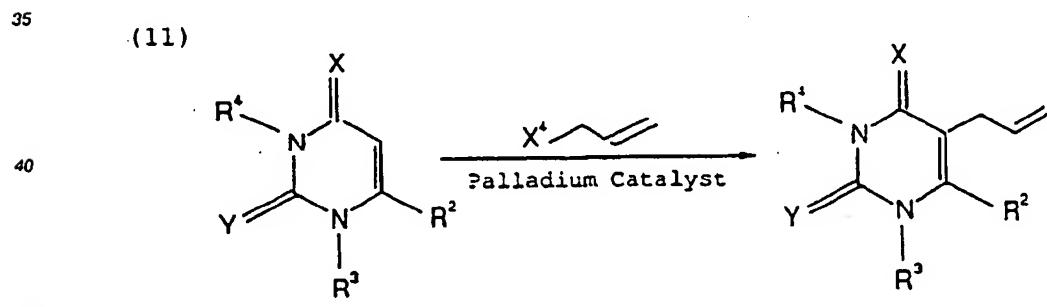
The reactions of the formulae (7) and (8) can be carried out in an amine solvent such as diethylamine and triethylamine in the presence of a palladium catalyst at an appropriate temperature of from room temperature to 70 °C. The reactions may be carried out more homogeneously by adding another solvent such as acetonitrile. As the catalyst, a palladium catalyst of bis(triphenylphosphine)palladium dichloride, tetrakis(triphenylphosphine)palladium(0) and bis(diphenylphosphino)ethane palladium dichloride can be used in combination with cuprous iodide.

The present compounds can be prepared also in accordance with the reaction formula (9) or (10) below, and the reactions may be carried out in the same manner as the reactions of the formulae (7) and (8) except that an olefin derivative of H<sub>2</sub>C=CH-R<sub>10</sub> wherein R<sub>10</sub> represents an alkoxy carbonyl, nitrile,

carbamoyl group and the like is used instead of the acetylene derivative in the reactions of the formulae (7) and (8):



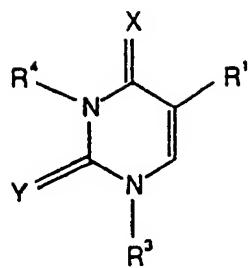
- 30 wherein the symbols have the same meanings as defined above.  
 The palladium catalyst may be the same as in the reaction of the formulae (7) and (8).  
 The compounds according to the invention can be prepared also in accordance with the reaction formula (11) below:



- 50 wherein  $X^4$  represents a halogen atom such as chlorine, bromine and iodine, and the other symbols have the same meaning as defined above.  
 The compounds according to the invention can be prepared also in accordance with the reaction formula (12) or (13) below:

(12)

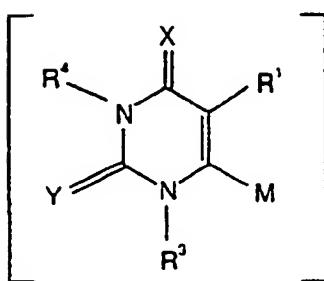
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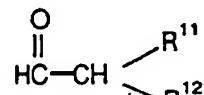
Organic Alkali Metal Compound

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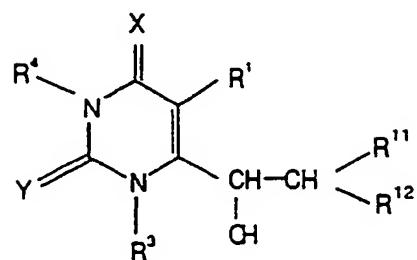


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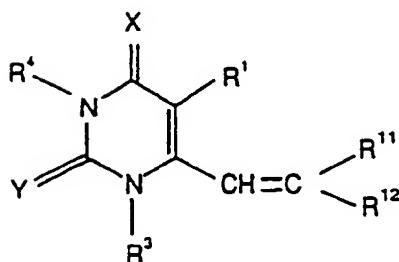
Dehydration



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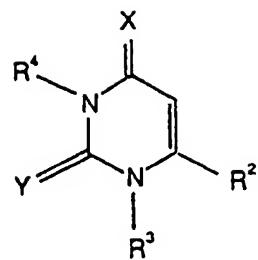


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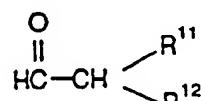
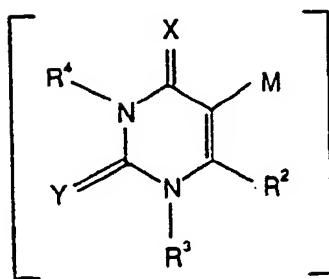
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Organic Alkali Metal Compound

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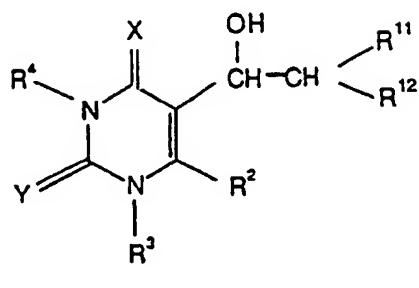
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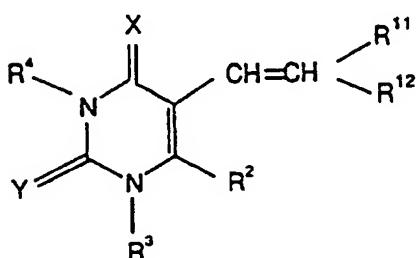
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Dehydration



wherein the symbols have the same meanings as defined hereinbefore.

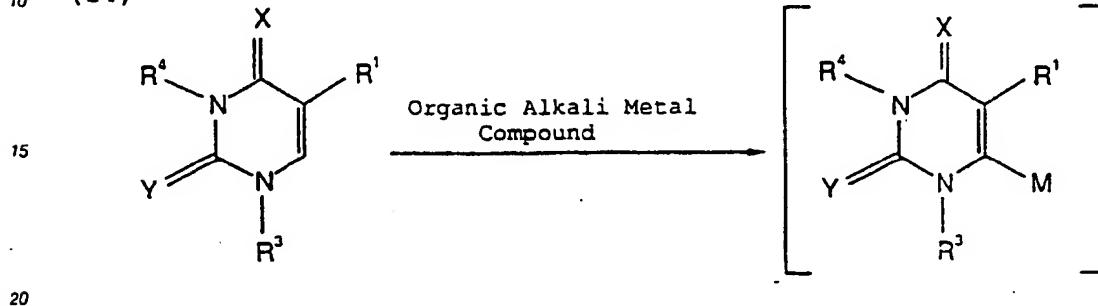
In the reactions of the formulae (12) and (13), intermediate compounds are prepared in accordance with the reaction formulae (1) and (2) as described hereinbefore except that a compound of  $OHC-CR(R^{11})(R^{12})$  wherein  $R^{11}$  and  $R^{12}$  independently represent a hydrogen atom, alkyl group such as methyl, ethyl and propyl or aryl group such as phenyl is used instead of the compounds  $R'X^2$  and  $R^2X^1$ , and then the intermediate compounds are dehydrated by a dehydrating agent such as mesyl chloride, tosyl chloride and thionyl chloride to produce the compounds according to the invention having an alkanyl group.

By hydrogenation, the alkynyl group of the compounds produced in the reactions of the formula (7) or (8) can be converted into the corresponding alkenyl or alkyl group and the alkenyl group of the compound produced in any one of the reactions formulae (9) to (13) can be converted into the corresponding alkyl group. For the reduction of alkynyl group into alkenyl group, the hydrogenation may be carried out at an appropriate temperature of from room temperature to 80°C under hydrogen atmosphere in the presence of

a catalyst such as palladium/barium sulfate, palladium/calcium carbonate, palladium/calcium carbonate/lead acetate and palladium/barium sulfate/quinoline in a solvent such as alcohol and acetic acid. For the reduction of alkenyl or alkynyl group into alkyl group, the hydrogenation may be carried out by using a catalyst such as palladium/carbon and palladium hydroxide under the same conditions as used for producing the alkenyl group.

5 The 6-benzyl substituted derivatives of the invention may be prepared in accordance with the reaction formula (14) below:

10 (14)



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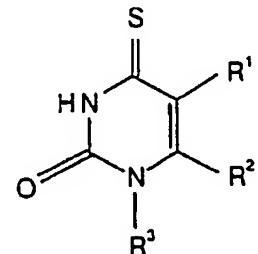
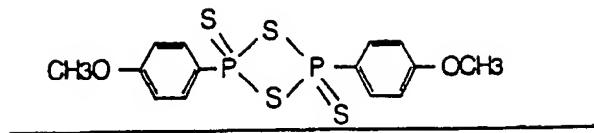
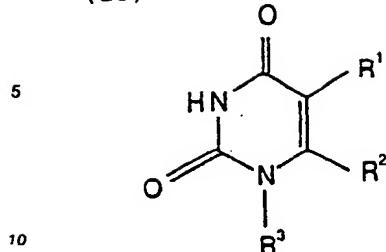
45 wherein the symbols have the same meanings as defined hereinbefore.

In the reactions of the formula (14), intermediate compounds are prepared in the same way as the reactions of the formula (1) using  $\text{OHC}-\text{R}^{13}$  where  $\text{R}^{13}$  represents an optionally substituted aryl group such as phenyl instead of  $\text{R}^1\text{X}^2$ , and the intermediate compounds are reduced by a suitable reducing agent to convert the hydroxyl group into a hydrogen atom. The reduction can be carried out by using hydrogen gas in the presence of palladium/carbon or palladium hydroxide.

50 The 6-substituted acyclouridine or acyclothymidine derivatives obtained in the above-described reactions can be converted into 4-thio derivatives by heating them with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide in a solvent such as toluene and xylene in accordance with the reaction formula (15) below:

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(15)

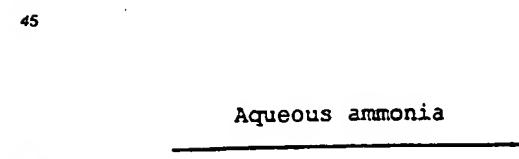
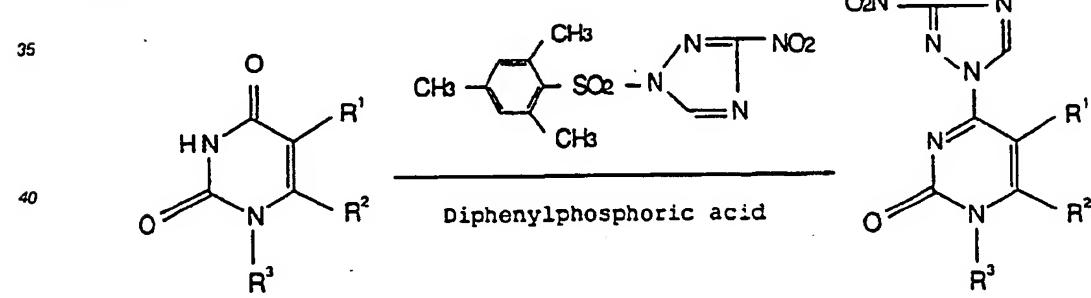


wherein the symbols have the same meanings as defined hereinbefore.

The 4-thio derivatives can be also prepared by preparing corresponding 4-chloro derivatives by chlorination of corresponding uridine or thymidine derivatives by a chlorinating agent such as phosphorous pertachloride or phosphorous oxychloride and reacting the 4-chloro derivatives with sodium bisulfide.

25 Further, 4-amino derivatives can be prepared by reacting the acyclouridine or thymidine derivatives with 1-(2-mesitylenesulfonyl)-3-nitro-1,2,4-triazole in the presence of diphenylphosphoric acid in a solvent such as pyridine to produce corresponding 4-(3-nitro-1,2,4-triazole) derivatives which are converted to the corresponding 4-amino derivatives by aqueous ammonia at an appropriate temperature of from room 30 temperature to 100 °C in accordance with the reaction formula (16) below:

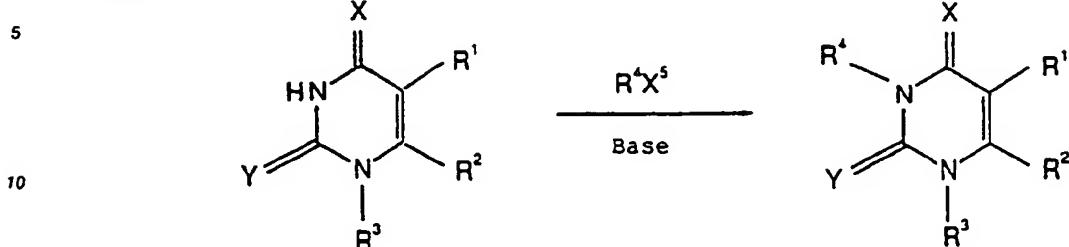
(16)



wherein the symbols have the same meanings as defined hereinbefore.  
Thus, the compounds of the invention represented by the formula I are prepared as described above.  
The above-obtained compounds where R4 is a hydrogen atom may be converted into corresponding

compounds having R<sup>4</sup> other than the hydrogen atom in accordance with the reaction formula (17) below:

(17)



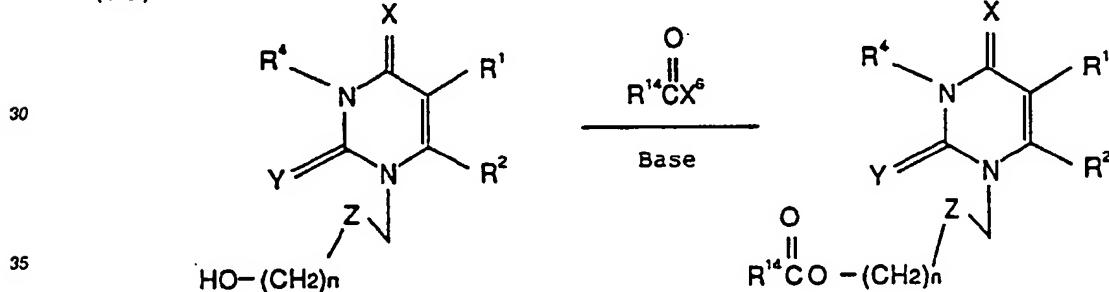
wherein X<sup>5</sup> represents a halogen atom such as chlorine, bromine and iodine or sulfonyloxy group such as toluenesulfonyloxy and mesyloxy, and the other symbols have the same meanings as defined hereinbefore.

The reaction of the formula (17) may be carried out in a suitable solvent such as tetrahydrofuran, acetonitrile, dimethylformamide, pyridine and alcohol in the presence of a base in an amount of 1 to 2 times of the starting compound at a suitable temperature from room temperature to the boiling point of the solvent. Examples of the base include sodium alkoxide, potassium alkoxide, potassium carbonate, sodium carbonate, sodium hydride and the like.

The compounds of the invention where R<sup>5</sup> is a hydroxyl group, which are obtained in any of the reactions of formula (1) to (17), may be converted into corresponding compounds having a substituted hydroxyl group in accordance with any of the reaction formulae (18) to (21) below:

25

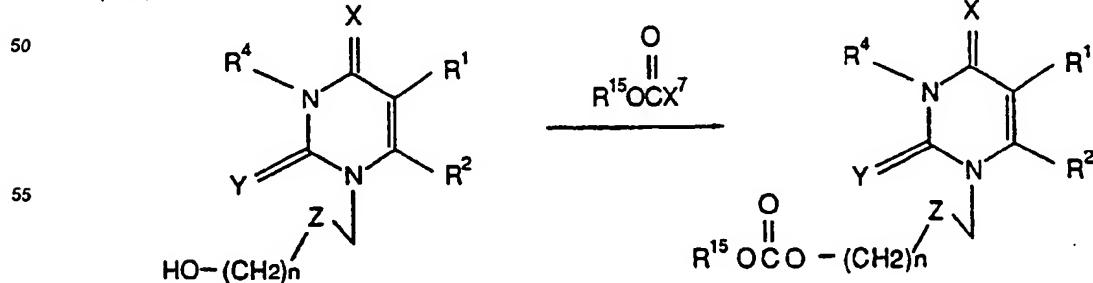
(18)



wherein R<sup>14</sup> represents an optionally branched alkyl group, optionally substituted aryl group or heterocyclic group, X<sup>6</sup> represents a halogen atom such as chlorine, bromine and iodine or -OCOR<sup>14</sup>, and the other symbols have the same meanings as defined hereinbefore.

The reaction of the formula (18) may be carried out in a suitable solvent such as tetrahydrofuran, acetonitrile, dimethylformamide, pyridine, dichloromethane and chloroform in the presence of a base in an amount of 1 to 2 times of the starting compound at a suitable temperature from room temperature to the boiling point of the solvent. Examples of the base include triethylamine, pyridine, imidazole, sodium carbonate, potassium carbonate, sodium hydroxide and the like.

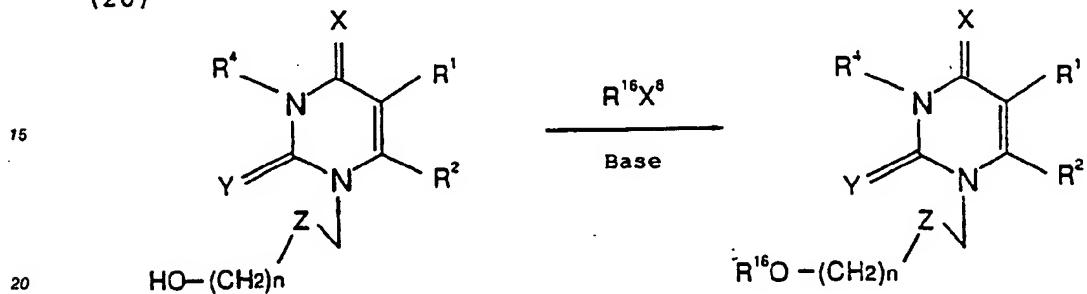
(19)



wherein  $R^{15}$  represents an optionally branched alkyl group or aralkyl group,  $X^7$  represents a halogen atom such as chlorine, bromine and iodine or  $-OCOOR^{15}$ , and the other symbols have the same meanings as defined hereinbefore.

The reaction of the formula (19) may be carried out in a suitable solvent such as tetrahydrofuran, 5 acetonitrile, dimethylformamide, pyridine, dichloromethane and chloroform in the presence of a base in an amount of 1 to 2 times of the starting compound at a suitable temperature from room temperature to the boiling point of the solvent. Examples of the base include triethylamine, pyridine, imidazole, sodium carbonate, potassium carbonate, sodium hydroxide and the like.

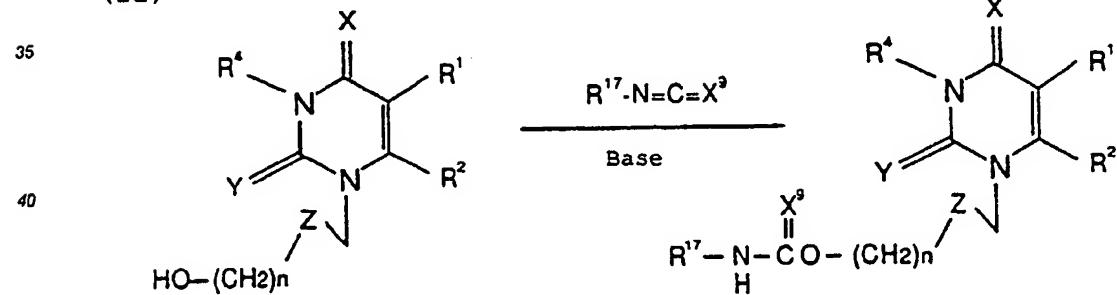
10 (20)



wherein  $R^{16}$  represents an optionally branched alkyl group or aralkyl group,  $R^8$  represents a halogen atom such as chlorine, bromine and iodine or sulfonyloxy group such as toluenesulfonyloxy and mesyloxy, and the other symbols have the same meanings as defined hereinbefore.

The reaction of the formula (20) may be carried out in a suitable solvent such as tetrahydrofuran, acetonitrile, dimethylformamide, pyridine, dichloromethane and chloroform in the presence of a base in an amount of 1 to 2 times of the starting compound at a suitable temperature from room temperature to the boiling point of the solvent. Examples of the base include triethylamine, pyridine, imidazole, sodium carbonate, potassium carbonate, sodium hydroxide and the like.

(21)



wherein  $R^{17}$  represents an optionally branched alkyl group or aryl group,  $X^3$  represents an oxygen or sulfur atom, and the other symbols have the same meanings as defined hereinbefore.

The reaction of formula (21) may be carried out in an appropriate solvent such as tetrahydrofuran, acetonitrile, dimethylformamide, pyridine, dichloromethane and chloroform at an appropriate temperature of from room temperature to the boiling point of the solvent.

The compounds of the present invention obtained as described hereinbefore and represented by the formula I or I' may be separated and purified by any of the conventional methods for the separation and purification of nucleosides, for example, recrystallization, adsorption chromatography, ion exchange chromatography and the like.

The compounds of the invention represented by the formula I or I' may be converted into a pharmaceutically acceptable salt thereof by a conventional method. Such salt may be, for example, an alkali metal salt such as sodium or potassium salt, alkaline earth metal salt such as magnesium salt, ammonium salt or alkylammonium salt such as methylammonium, dimethylammonium, triethylammonium,

tetramethylammonium salt or the like.

The compounds according to the invention can be administered to human beings via any route, oral, rectal, parenteral or local for the prevention or treatment of the infection of viruses such as retrovirus. The administration dose of the compounds according to the invention may be determined according to age, physical condition, body weight and the like of a patient to be treated; however, a suitable daily dose of the compounds is 1 to 100 mg/(body weight)kg, preferably 5 to 50 mg/(body weight)kg and it is administered in one to several times.

The compound of the invention is generally prepared in a pharmaceutical composition with a suitable carrier, excipient and other additives. Either a liquid carrier or solid carrier may be suitably used for the present antiviral agent.

Examples of the solid carrier are lactose, kaolin, sucrose, crystalline cellulose, corn starch, talc, agar, pectin, stearic acid, magnesium stearate, lecithin, sodium chloride and the like.

Examples of the liquid carrier are glycerin, peanut oil, polyvinyl pyrrolidone, olive oil, ethanol, benzyl alcohol, propylene glycol, water and the like.

The present antiviral agent may be made in various forms. For example, it may be in the form of a tablet, powder, granule, capsule, suppository, troche or the like when a solid carrier is used, and it may be also in the form of syrup, emulsion, soft gelatin capsule, cream, gel, paste, spray, injection solution, or the like when a liquid carrier is used.

The novel 6-substituted acyclopyrimidine nucleoside derivatives according to the present invention have an effective antiviral activity against viruses such as retrovirus and have a relatively low toxicity against the host cell, hence the derivatives of the invention are extremely useful as an active ingredient of antiviral agent.

25

#### EXAMPLE

The present invention will be further illustrated hereinafter by way of examples, but these examples do not limit the invention and many variations and modifications can be made without departing from the scope of the present invention.

The numbers of the compounds used in the description of the examples correspond to those used in Table 1.

The starting compounds used in the examples such as

1-[(2-hydroxyethoxy)methyl]-6-phenylthio-2-thiothymine,  
 35 1-[(2-hydroxyethoxy)methyl]-6-phenylthiothymine,  
 1-[(2-hydroxyethoxy)methyl]-6-(m,m'-dimethylphenylthio)-thymine,  
 1-[(2-hydroxyethoxy)methyl]-6-(m,m'-dimethylphenylthio)-2-thiothymine,  
 1-[(2-hydroxyethoxy)methyl]-6-(m,m'-dichlorophenylthio)thymine,  
 1-[(2-hydroxyethoxy)methyl]-6-benzylthymine,  
 40 1-[(2-hydroxyethoxy)methyl]-6-cyclohexylthiothymine,  
 1-[(2-hydroxyethoxy)methyl]-6-m-tolylthiothymine  
 and the like were produced according to the methods described in the examples of PCT International Application WO89/09213.

45

#### EXAMPLE 1

Preparation of 1-[(2-acetoxyethoxy)methyl]-6-phenylthio-2-thiothymine (compound No.1)

50

To 2 ml of pyridine, 0.31 g (1.0 mmole) of 1-[(2-hydroxyethoxy)methyl]-6-phenylthio-2-thiothymine and 0.10 ml (1.1 mmole) of acetic anhydride were added under a flow of nitrogen, allowed to react for 2 hours at room temperature, concentrated to dryness under reduced pressure and crystallized from ethanol/water to obtain 0.62 g of the target compound (Yield: 88 %).

55

#### EXAMPLES 2 - 6

Using the following compounds in place of 1-[(2-hydroxyethoxy)methyl]-6-phenylthio-2-thiothymine in Example 1, Compounds Nos.2 to 6 in Table 1 were obtained in the same manner as Example 1:

- 1-[(2-hydroxyethoxy)methyl]-6-phenylthiothymine,  
 1-[(2-hydroxyethoxy)methyl]-6-(m,m'-dimethylphenylthio)thymine,  
 5 1-[(2-hydroxyethoxy)methyl]-6-(m,m'-dimethylphenylthio)-2-thiothymine,  
 1-[(2-hydroxyethoxy)methyl]-6-(m,m'-dichlorophenylthio)thymine, and  
 1-[(2-hydroxyethoxy)methyl]-6-benzylthymine.

10 EXAMPLES 7 - 13

Compounds Nos.7 to 13 in Table 1 were prepared in the same manner as Example 2 by using ethyl formate, i-butyryl chloride, pivaloyl chloride, decanoyl chloride, cyclohexanecarbonyl chloride, benzoyl chloride or nicotinyl chloride respectively in place of acetic anhydride in Example 2.

15

EXAMPLE 14

Compound No.14 was prepared in the same manner as Example 2 by using t-butoxycarbonyl chloride 20 in place of acetic anhydride in Example 2.

EXAMPLE 15

25 Compound No.15 was obtained in the same manner as Example 2 by using 1-[(2-hydroxyethoxy)-methyl]-6-cyclohexylthiothymine and benzyloxycarbonyl chloride in place of 1-[(2-hydroxyethoxy)methyl]-6-phenylthiothymine and acetic anhydride in Example 2 respectively.

30 EXAMPLE 16

Preparation of 1-[(2-phenylcarbamoyloxyethoxy)methyl]-6-m-tolylthiothymine (Compound No.16)

35 To 2 ml of pyridine, 0.32 g (1.0 mmole) of 1-[(2-hydroxyethoxy)methyl]-6-m-tolylthiothymine and 0.12 ml (1.1 mmole) of phenyl isocyanate were added under a flow of nitrogen, allowed to react for 18 hours at room temperature. The reaction mixture was concentrated to dryness under reduced pressure and crystallized from acetone/water to obtain 0.24 g of the target compound (Yield: 54 %).

40

EXAMPLE 17 and 18

Compounds Nos.17 and 18 were prepared in the same manner as Example 16 by using ethyl isocyanate or phenyl thioisocyanate respectively in place of phenyl isocyanate.

45

EXAMPLE 19

50 Preparation of 1-[(2-benzyloxyethoxy)methyl]-6-phenylthiothymine (Compound No.19)

To 4 ml of tetrahydrofuran, 0.17 g (4.2 mmol) of sodium hydride was added under a nitrogen flow, and stirred to form a suspension. To this suspension, a solution of 0.62 g (2.0 mmole) of 1-[(2-hydroxyethoxy)-methyl]-6-phenylthiothymine in 2 ml of tetrahydrofuran was added slowly to react for 45 minutes at room 55 temperature. The resultant was added with 0.24 ml (2.0 mmol) of benzyl bromide and 7.4 g (20  $\mu$ mol) of tetrabutylammonium iodide and allowed to react for 15 hours. The reaction mixture was neutralized with acetic acid and distributed between chloroform and saturated aqueous solution of sodium hydrogencarbonate, and the chloroform layer was concentrated to dryness under reduced pressure. The residue was

dissolved in a small amount of chloroform, adsorbed on a silica gel column and eluted with 1 % methanol/chloroform. The eluate was concentrated and crystallized from diethyl ether/hexane to obtain 0.64 g of the target compound (Yield: 80 %).

5

#### EXAMPLES 20 - 21

Compounds Nos.20 and 21 were prepared in the same manner as Example 19 by using methyl bromide or bromopentane respectively in place of benzyl bromide.

10

#### EXAMPLE 22

##### 15 Preparation of 1-(methoxymethyl)-6-phenylthiothymine (Compound No.22)

To 250 ml of methylene chloride, 25 g (0.20 mol) of thymine and 109 ml (0.44 mol) of bistrimethylsilylacetamide were added under a nitrogen flow, and stirred for 2.5 hours at room temperature. To this mixture, 24 g (0.30 mole) of chloromethyl methyl ether and 0.59 g (1.6 mmol) of tetrabutylammonium iodide were added and heated under reflux for 1.5 hours. Then, the reaction mixture was added with 400 ml of methanol and 100 ml of water slowly and concentrated under reduced pressure. The residue was crystallized from ethyl acetate to obtain 1-(methoxymethyl)-thymine. Then, 119 ml of lithium diisopropylamide (0.25 mol) solution in tetrahydrofuran (2.1 M) was added to 335 ml of tetrahydrofuran under a nitrogen flow at -70 °C, to which a suspension of 17.0 g (0.10 ml) 1-(methoxymethyl)thymine in 107 ml of tetrahydrofuran was added dropwise over 30 minutes. After stirring for 2.5 hours at -70 °C, the reaction mixture was added with a solution of 43.6 g of diphenyl disulfide in 49 ml of tetrahydrofuran dropwise over 20 minutes and allowed to react for 20 minutes. The reaction mixture was added with 35 ml of acetic acid, brought to room temperature and then added with 1 l of ethyl acetate. The mixture was washed with water (100 ml x 5) and saturated solution of sodium hydrogencarbonate (twice), dried on magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from ethanol to obtain 20 g of the target compound (Yield: 73 %).

#### EXAMPLES 23 - 26

35

Compounds Nos.23 to 26 were prepared in the same manner as Example 22 by using 1-(ethoxymethyl)thymine, 1-[(2-azidoethoxy)methyl]thymine, 1-[(2-fluoroethoxy)methyl]thymine or 1-[(2-chloroethoxy)methyl]thymine respectively in place of 1-(methoxymethyl)thymine.

40

#### EXAMPLE 27

##### Preparation of 6-phenylthiothymine (Compound No.27)

45

To 100 ml of concentrated hydrochloric acid, 17.2 g (62 mmole) of 1-(methoxymethyl)-6-phenylthiothymine was added and allowed to react for 2 hours at 80 °C. The reaction mixture was concentrated under reduced pressure and crystallized from ethanol to obtain 3.8 g of the target compound (Yield: 26 %).

50

#### EXAMPLE 28

##### Preparation of 1-methyl-6-phenylthiothymine (Compound No.28)

55

To 1 ml of dimethyl sulfoxide, 20 mg (85 μmol) of 6-phenylthiothymine, 2.5 μl (40 μmol) of methyl iodide and 12 mg (85 μmol) of potassium carbonate were added and allowed to react for 6 hours at 80 °C. The reaction mixture was concentrated under reduced pressure and adsorbed in a silica gel column and

eluted with 1 % methanol/chloroform. The eluate was concentrated and crystallized from diisopropyl ether to obtain 5.0 mg of the target compound (Yield: 51 %).

5 EXAMPLES 29 - 30

Compounds Nos.29 and 30 were prepared in the same manner as Example 28 by using ethyl tosylate or n-butyl iodide respectively in place of methyl iodide.

10 EXAMPLE 31

Preparation of 1-(4-hydroxybutyl)-6-phenylthiothymine (Compound No.31)

15 To 2 ml of dimethyl sulfoxide, 468 mg (2.0 mmol) of 6-phenylthiothymine, 358 mg (1.0 mmol) of 4-*t*-butyldimethylsiloxy)-butyl-p-toluenesulphonate and 276 mg (2.0 mmol) of potassium carbonate were added and heated to react for 4 hours at 80 °C. The reaction mixture was concentrated under reduced pressure, added with methanol and filtered. The filtrate was concentrated under reduced pressure, added with 20 ml of tetrahydrofuran and 1 ml of 1 N hydrochloric acid and stirred for 90 minutes. The reaction mixture was concentrated under reduced pressure and adsorbed on a silica gel column and eluted with 2 % methanol/chloroform. The eluate was concentrated and crystallized from acetone/hexane to obtain 12.0 mg of the target compound (Yield: 4 %).

25 EXAMPLE 32

Preparation of 1-(methylthiomethyl)-6-phenylthiothymine (Compound No.32)

30 To 4 ml of dimethylformamide, 0.17 ml (2.0 mmol) of chloromethylmethylsulfide, 0.47 g (2.0 mmol) of 6-phenylthiothymine, 0.56 ml (2.0 mmol) of triethylamine were added and allowed to react for 22 hours at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was adsorbed on a silica gel column and eluted with chloroform. The eluate was concentrated and crystallized from ethyl acetate to obtain 45 mg of the target compound (Yield: 8 %).

EXAMPLE 33

40 Preparation of 1-[(2-hydroxyethoxy)methyl]-3-benzyl-6-phenylthiothymine (Compound No.33)

45 To 2 ml of dimethylformamide, 0.62 g (2.0 mmol) of 1-[(2-hydroxyethoxy)methyl]-6-phenylthiothymine, 0.26 ml (2.2 mmol) of benzyl bromide and 0.38 ml (2.2 mmol) of ethyldiisopropylamine were added and allowed to react for 5 days at room temperature under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure and the residue was adsorbed on a silica gel column and eluted with 1 % methanol/chloroform to obtain 0.24 g of the target compound (Yield: 30 %).

50 EXAMPLE 34

Compounds No.34 was prepared in the same manner as Example 33 by using methyl iodide in place of benzyl bromide.

55 EXAMPLE 35

## Preparation of 1-ethoxymethyl-5-ethyl-6-phenylthiouracil (Compound No.247)

To 100 ml of methylene chloride, 5.1 g (40 mmol) of 5-ethyluracil and 22 ml (0.88 mmol) of bistrimethylsilylacetamide were added under a nitrogen atmosphere and stirred for 40 minutes at room temperature. To this mixture, 4.1 ml (88 mmole) of chloromethyl ethyl ether and 0.15 g (0.4 mmol) of tetrabutylammonium iodide were added and heated under reflux for 15 hours. Then, the reaction mixture was poured carefully into 50 ml of saturated aqueous solution of sodium hydrogencarbonate and filtered through Celite. The organic layer was washed with water, dried on magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from ethyl acetate to obtain 6.4 g of 1-ethoxymethyl-5-ethyluracil (Yield: 81%).

Then, 2.2 ml of lithium diisopropylamide (4.4 mmol) solution in tetrahydrofuran (2.1 M) was added to 6 ml of tetrahydrofuran under a nitrogen atmosphere at -70 °C, to which a solution of 0.40 g (2.0 mmol) of 1-ethoxymethyl-5-ethyluracil in 3 ml of tetrahydrofuran was added dropwise over 15 minutes. After stirring for 1 hour at -70 °C, the reaction mixture was added with a solution of 0.57 g of diphenyl disulfide in 2 ml of tetrahydrofuran dropwise over 10 minutes and allowed to react for 30 minutes. The reaction mixture was added with 1 ml of acetic acid, brought to room temperature and then added with 30 ml of ethyl acetate. The mixture was washed with water (3 ml x 5) and saturated aqueous solution of sodium hydrogencarbonate (twice), dried on magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane = 3:17) and crystallized from ethyl acetate to obtain 0.61 g of 1-ethoxymethyl-5-ethyl-6-phenylthiouracil (Yield: 32 %).

## EXAMPLE 36

Compound No.357 was obtained in the same way as Example 35 by using 3,3',5,5'-tetramethylphenyl disulfide in place of diphenyl disulfide.

## EXAMPLE 37

30

## Preparation of 1-ethoxymethyl-5-ethyl-6-phenylthio-2-thiouracil (Compound No.358)

To 100 ml of methylene chloride, 5.1 g (40 mmol) of 2-thiouracil and 22 ml (0.88 mmol) of bistrimethylsilylacetamide were added under a nitrogen atmosphere, and stirred for 40 minutes at room temperature. To this mixture, 8.2 ml (88 mmole) of chloromethyl ethyl ether and 0.15 g (0.4 mmol) of tetrabutylammonium iodide were added and heated under reflux for 15 hours. Then, the reaction mixture was poured carefully into 50 ml of saturated aqueous solution of sodium hydrogencarbonate and filtered through Celite. The organic layer was washed with water, dried on magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from ethyl acetate to obtain 1.1 g of 1-ethoxymethyl-2-thiouracil (Yield: 15 %).

Then, 3.3 ml of lithium diisopropylamide solution in tetrahydrofuran (2.1 M) was added to 9 ml of tetrahydrofuran under a nitrogen atmosphere at -70 °C, to which a solution of 0.56 g (3.0 mmol) of 1-ethoxymethyl-2-thiouracil in 3 ml of tetrahydrofuran was added dropwise over 15 minutes. After stirring for 1 hour at -70 °C, the reaction mixture was added with a solution of 0.85 g (3.9 mmol) of diphenyl disulfide in 1 ml of tetrahydrofuran dropwise over 10 minutes and allowed to react for 20 minutes. The reaction mixture was added with 1 ml of acetic acid, brought to room temperature and then added with 30 ml of ethyl acetate. The mixture was washed with water (3 ml x 5) and saturated aqueous solution of sodium hydrogencarbonate (twice), dried on magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane = 3:17), crystallized from ethyl acetate to obtain 0.64 g of 1-ethoxymethyl-6-phenylthio-2-thiouracil (Yield: 73 %).

Then, 2.1 ml of 1.6 M butyl lithium (3.4 mmol) solution in hexane was added to a solution of 0.57 ml (3.4 mmol) 2,2,6,6-tetramethylpyperidine in 8 ml of tetrahydrofuran under a nitrogen atmosphere at -70 °C, warmed to -50 °C, and stirred for 20 minutes. After cooling to -70 °C again, the mixture was added with a solution of 0.44 g (1.5 mmol) of 1-ethoxymethyl-6-phenylthio-2-thiouracil in 4 ml tetrahydrofuran dropwise over 15 minutes, stirred for an hour, added with 1.2 ml (15 mmol) ethyl iodide and stirred for 19 hours. Then, the mixture was added with 1 ml acetic acid, brought to room temperature, added with 30 ml ethyl acetate, washed with water and saturated aqueous solution of sodium chloride, dried on magnesium sulfate

and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane = 3:17) and crystallized from ethyl acetate to obtain 96 mg of the title compound (Yield: 20 %).

5                   EXAMPLE 38

Compound No.359 was prepared in the same way as Example 37 by using 3,3',5,5'-tetramethyldiphenyl disulfide in place of diphenyl disulfide.

10                   EXAMPLE 39

Compound No.360 was prepared in the same way as Example 35 by using benzyl chloromethyl ether in place of chloromethyl ethyl ether.

EXAMPLE 40

20                   Compound No.361 was prepared in the same way as Example 35 by using benzyl chloromethyl ether and 3,3',5,5'-tetramethyldiphenyl disulfide respectively in place of chloromethyl ethyl ether and diphenyl disulfide.

25                   EXAMPLE 41

Compound No.362 was prepared in the same way as Example 35 by using thymine and benzyl chloromethyl ether in place of 5-ethyluracil and chloromethyl ethyl ether.

30                   EXAMPLE 42

Compound No.41 was prepared in the same way as Example 22 by using chloromethyl propyl ether in place of chloromethyl methyl ether.

35                   EXAMPLE 43

40                   Compound No.485 was prepared in the same way as Example 22 by using butyl chloromethyl ether in place of chloromethyl methyl ether.

EXAMPLE 44

45                   Compound No.365 was prepared in the same way as Example 35 by using 3,3',5,5'-tetrachlorodiphenyl disulfide in place of diphenyl disulfide.

EXAMPLE 45

50                   Compound No.366 was prepared in the same way as Example 35 by using 5-ethyl-2-thiouracil and 3,3',5,5'-tetrachlorodiphenyl disulfide respectively in place of 5-ethyluracil and diphenyl disulfide.

55                   EXAMPLE 46

Compound No.496 was prepared in the same way as Example 35 by using 5-isopropyluracil in place of 5-ethyluracil.

EXAMPLE 47

Compound No.497 was prepared in the same way as Example 35 by using 5-isopropyl-2-thiouracil in place of 5-ethyluracil.

5

EXAMPLE 48

Compound No.574 was prepared in the same way as Example 35 by using 5-cyclopropyluracil in place of 5-ethyluracil.

EXAMPLE 49

15 Compound No.575 was prepared in the same way as Example 35 by using 5-cyclopropyl-2-thiouracil in place of 5-ethyluracil.

EXAMPLE 50

20

Compound No.675 was prepared in the same way as Example 35 by using chloromethyl isopropyl ether in place of chloromethyl ethyl ether.

25 EXAMPLE 51

Compound No.676 was prepared in the same way as Example 35 by using 5-ethyl-2-thiouracil and chloromethyl isopropyl ether respectively in place of 5-ethyluracil and chloromethyl ethyl ether.

30

EXAMPLE 52

Compound No.685 was prepared in the same way as Example 35 by using chloromethyl cyclohexyl ether in place of chloromethyl ethyl ether.

35

EXAMPLE 53

Compound No.686 was prepared in the same way as Example 35 by using 5-ethyl-2-thiouracil and chloromethyl cyclohexyl ether respectively in place of 5-ethyluracil and chloromethyl ethyl ether.

EXAMPLE 54

45

Compound No.689 was prepared in the same way as Example 35 by using chloromethyl cyclohexyl-methyl ether in place of chloromethyl ethyl ether.

EXAMPLE 55

50

Compound No.690 was prepared in the same way as Example 35 by using 5-ethyl-2-thiouracil and chloromethyl cyclohexylmethyl ether respectively in place of 5-ethyluracil and chloromethyl ethyl ether.

55 EXAMPLE 56

Compound No.512 was prepared in the same way as Example 35 by using 5-isopropyluracil and benzyl chloromethyl ether respectively in place of 5-ethyluracil and chloromethyl ethyl ether.

## EXAMPLE 57

Compound No.513 was prepared in the same way as Example 35 by using 5-isopropyl-2-thiouracil and benzyl chloromethyl ether respectively in place of 5-ethyluracil and chloromethyl ethyl ether.

5

## EXAMPLE 58

Compound No.748 was prepared in the same way as Example 35 by using chloromethyl phenetyl ether in place of chloromethyl ethyl ether.

## EXAMPLE 59

15 Compound No.749 was prepared in the same way as Example 35 by using 5-ethyl-2-thiouracil and chloromethyl phenetyl ether respectively in place of 5-ethyluracil and chloromethyl ethyl ether.

## EXAMPLE 60

20 Compound No.372 was prepared in the same way as Example 35 by using 5-ethyl-2-thiouracil and chloromethyl 4-methylbenzyl ether respectively in place of 5-ethyluracil and chloromethyl ethyl ether.

## EXAMPLE 61

Compound No.704 was prepared in the same way as Example 35 by using 5-ethyl-2-thiouracil and 4-chlorobenzyl chloromethyl ether respectively in place of 5-ethyluracil and chloromethyl ethyl ether.

30

## EXAMPLE 62

## Preparation of 6-benzyl-1-ethoxymethyl-5-ethyluracil (Compound No.472)

35

To 100 ml of methylene chloride, 5.1 g (40 mmol) of 5-ethyluracil and 22 ml (88 mmol) of bistrimethylsilylacetamide were added under a nitrogen atmosphere and stirred for 40 minutes at room temperature. To this mixture, 4.1 ml (88 mmole) of chloromethyl ethyl ether and 0.15 g (0.4 mmol) of tetrabutylammonium iodide were added and heated under reflux for 15 hours. Then, the reaction mixture was poured into 50 ml of saturated sodium bicarbonate solution carefully and filtered through Celite. The organic layer was washed with water, dried on magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from ethyl acetate to obtain 6.4 g of 1-ethoxymethyl-5-ethyluracil (Yield: 81 %).

Then, 2.2 ml (4.4 mmol) of lithium diisopropylamide solution in tetrahydrofuran (2.1 M) was added to 45 ml of tetrahydrofuran under a nitrogen atmosphere at -70 °C, to which a solution of 0.40 g (2.0 mmol) of 1-ethoxymethyl-5-ethyluracil in 3 ml of tetrahydrofuran was added dropwise over 15 minutes. After stirring for 1 hour at -70 °C, the reaction mixture was added with a solution of 0.27 g (2.6 mmol) of benzaldehyde in 2 ml of tetrahydrofuran dropwise over 10 minutes and allowed to react for 30 minutes. The reaction mixture was added with 1 ml of acetic acid, brought to room temperature and then added with 30 ml of ethyl acetate. The mixture was washed with water (3 ml x 5) and saturated aqueous solution of sodium hydrogencarbonate (twice), dried on magnesium sulfate and concentrated under reduced pressure.

The residue was dissolved in 10 ml of ethanol, added with 20 mg of 20 % palladium hydroxide/carton and stirred under a hydrogen atmosphere for a day at 55 °C. Then, after removing the catalyst by filtration, the reaction mixture was concentrated. The residue was crystallized from hexane to obtain 0.28 g of 6-benzyl-1-ethoxymethyl-5-ethyluracil (Yield: 85 %).

## EXAMPLE 63

Compound No.474 was prepared in the same way as Example 62 by using 3,5-dimethylbenzaldehyde in place of benzaldehyde.

5 EXAMPLE 64

Preparation of 1-butyl-5-ethyl-6-phenylthiouracil (Compound No.252)

10 To a solution of 5.6 g (40 mmol) of 5-ethyluracil in 60 ml of dimethylformamide, 5.5 g (40 mmol) of potassium carbonate and 2.3 ml (20 mmol) of *n*-iodobutane were added and stirred for 2 hours at 120 °C. The reaction mixture was concentrated under reduced pressure and distributed between dichloromethane and aqueous solution of ammonium chloride, and the organic layer was concentrated under reduced pressure. The residue was adsorbed on a silica gel column and eluted with 30 % ethyl acetate/hexane to obtain 2.7 g of 1-butyl-5-ethyluracil (Yield: 69 %).

15 Then, a solution of 4.4 mmol of lithium diisopropylamide in 2.8 ml of tetrahydrofuran was added dropwise to a solution of 392 mg (2.0 mmol) 1-butyl-5-ethyluracil in 9 ml of tetrahydrofuran under a nitrogen atmosphere at -70 °C and stirred for 70 minutes at -70 °C and further 5 minutes at -25 °C. The mixture was cooled to -70 °C again, added with a solution of 567 mg (2.6 mmol) diphenyl disulfide in 3 ml of 20 tetrahydrofuran, stirred for 20 minutes, added with 1 ml of acetic acid, brought to room temperature, washed with saturated aqueous solution of sodium chloride and concentrated under reduced pressure. The residue was adsorbed on a silica gel, eluted with 10 % ethyl acetate/hexane and crystallized from hexane to obtain 40 mg of 1-butyl-5-ethyl-6-phenylthiouracil (Yield: 7 %).

25 EXAMPLE 65

Compound No.363 was prepared in the same way as Example 35 by using 5-ethyl-2-thiouracil and benzyl chloromethyl ether respectively in place of 5-ethyluracil and chloromethyl ethyl ether.

30

EXAMPLE 66

Compound No.364 was prepared in the same way as Example 35 by using 5-ethyl-2-thiouracil, benzyl 35 chloromethyl ether and 3,3',5,5'-tetramethyldiphenyl disulfide respectively in place of 5-ethyluracil, chloromethyl ethyl ether and diphenyl disulfide.

EXAMPLE 67

40

Preparation of 5-(2-(*E*)-bromovinyl)-1-(ethoxymethyl)-6-(phenylthio)uracil (Compound No.270)

In 50 ml of dichloromethane, 4.76 g (20 mmol) of 5-iodouracil was suspended and added with 11 ml (45 mmol) of bistrimethylsilylacetamide and stirred for 15 minutes at room temperature to form a homogeneous solution. This solution was added with 2.04 ml (22 mmol) of chloromethyl ethyl ether and 60 mg of tetra-*n*-butylammonium iodide and heated under reflux for 3 hours. After the solvent was evaporated under reduced pressure, the residue was added with water to produce crystals, which were taken by filtration. The crystals were washed by suspending them in hot methanol and recovering them by cooling and filtration to obtain 50 5.43 g of 1-(ethoxymethyl)-5-iodouracil.

Then, 1.184 g (4 mmol) of 1-(ethoxymethyl)-5-iodouracil, 870 µg (8 mmol) of ethyl acrylate, 45 mg of palladium acetate and 0.6 ml of triethylamine were dissolved in 40 ml of dimethylformamide, heated and stirred for 5 hours at 70 °C. After the solvent was evaporated under reduced pressure, the residue was adsorbed on a silica gel column, eluted with a solution of dichloromethane/ethyl acetate (1:1 v/v) to recover 55 the desired fraction, from which the solvent was evaporated under reduced pressure to obtain 798 mg of 5-(2-(*E*)-carboethoxyvinyl)-1-(ethoxymethyl)uracil as crystals.

Then, 0.16 g (4.0 mmol) of sodium hydroxide and 0.54 g (2.0 mmol) of 5-(2-(*E*)-carboethoxyvinyl)-1-(ethoxymethyl)uracil were added to 8 ml of water, stirred for 4.5 hours, neutralized with 1N hydrochloric

acid and added with 10 ml of dimethylformamide to obtain a homogeneous solution.

This solution was then added with 0.62 g (4.5 mmol) of potassium carbonate, stirred for 5 minutes at room temperature to make it a homogeneous solution, then added with 0.36 g (2.0 mmol) of N-bromosuccinimide and stirred for 30 minutes. The reaction mixture was concentrated under reduced

5 pressure and distributed between chloroform and aqueous solution of ammonium chloride, and the organic layer was concentrated under reduced pressure. The residue was adsorbed on a silica gel column and eluted with 20 % ethyl acetate/hexane to collect the desired fraction, from which the solvent was evaporated under reduced pressure to obtain 0.15 g of 5-(2-(E)-bromovinyl)-1-(ethoxymethyl)uracil (Yield: 28 %).

10 Then, a solution of 0.15 g (0.56 mmol) 5-(2-(E)-bromovinyl)-1-(ethoxymethyl)uracil in 1.7 ml of tetrahydrofuran was added dropwise to a solution of 1.22 mmol of lithium diisopropylamide in 2.3 ml of tetrahydrofuran under a nitrogen atmosphere at -70 °C over 7 minutes and stirred for 40 minutes, added with a solution of 0.16 g (0.73 mmol) diphenyl disulfide in 1 ml of tetrahydrofuran and stirred for 1 hour. The reaction mixture was washed with saturated aqueous solution of sodium chloride and concentrated under reduced pressure. The residue was adsorbed on a silica gel column, eluted with 15 % ethyl acetate/hexane 15 to collect the desired fraction, from which the solvent was evaporated under reduced pressure to obtain 11 mg of the target compound (Yield: 5 %, m.p.: 143 - 148 °C).

15 Compounds No.35 to 40, 42 to 246, 248 to 251, 253 to 269, 271 to 356, 367 to 371, 373 to 471, 473, 475 to 484, 486 to 495, 498 to 511, 514 to 573, 576 to 674, 677 to 684, 687, 688, 691 to 703, 705 to 747 and 750 to 803 in Table 1 may be prepared similarly according to the methods described in the working 20 examples above.

## EXAMPLE 68

25

Production of tablet

30	1-[(2-acetoxyethoxy)methyl]-6-phenylthiothymine	10 g
	Corn starch	65 g
35	Carboxycellulose	20 g
	Polyvinyl pyrrolidone	3 g
	<u>Calcium stearate</u>	<u>2 g</u>
40	<b>Total weight</b>	<b>100 g</b>

45 The above-mentioned components were well mixed and tablets were produced by a direct tableting method. Each tablet had a weight of 100 mg and contained 1.0 mg of 1-[(2-acetoxyethoxy)methyl]-6-phenylthiothymine.

## EXAMPLE 69

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## Production of powder and encapsulated medicine

5	1-[(2-acetoxyethoxy)methyl]-6-phenylthiothymine	20 g
	<u>Crystalline cellulose</u>	<u>80 g</u>
10	Total weight	100 g

Both powder components were well mixed to obtain a powder formulation. 100 mg of the thus-obtained powder was charged into a hard capsule of No.5 to obtain an encapsulated medicine.

15  
EXAMPLE 70

## Inhibitory activity for HIV infection

20  
In RPMI 1640 DM culture medium containing 20 mM of Hepes buffer solution, 10 % fetal bovine serum and 20 g/ml of gentamycin,  $3 \times 10^4$  MT-4 cells (human T cell clone which is destroyed by the infection of HIV) were infected with HIV in an amount of 100 times as large as expected to cause 50 % infection of the cells. Immediately thereafter, a predetermined amount of sample was added to the culture medium using 50 mg/ml sample solutions in dimethyl sulfoxide and the cells were cultured at 37°C.

25  
After 5 days of incubation, the number of existing cells was counted to determine the concentration of the compound for preventing the death of 50 % of the MT-4 cells. Separately, MT-4 cells were cultured in the same way as above except that they were not infected with HIV to determine the concentration of the compound at which 50 % of the MT-4 cells were destroyed.

30  
Both results are shown in Table 2.

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50

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Table 2

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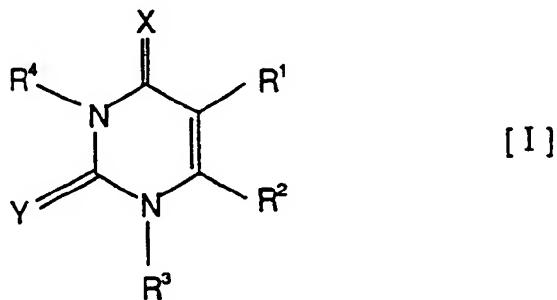
10	Compound No.	50% inhibitory concentration of HIV infection (μM)	50% cytotoxic concentration to MT-4 cells (μM)
15	1	2.8	196
20	2	6.7	314
25	3	< 0.8	236
30	4	< 0.8	240
35	5	1.8	218
40	7	7.1	292
45	8	9.9	218
50	10	11	162
55	11	7.5	78
	12	7.6	53
	13	11	170
	14	12	66
	16	21	420
	17	0.96	171
	20	8.6	292
	22	2.1	244
	23	< 0.8	215
	24	5.7	169
	25	1.1	191
	26	1.7	193
	29	4.3	96

5	Compound No.	50% inhibitory concentration of HIV infection (µM)	50% cytotoxic concentration to MT-4 cells (µM)
10	30	1.2	89
	31	13	249
	32	1.2	154
15	41	5.6	147
	247	0.016	133
20	252	0.016	45
	357	0.005	> 100
	358	0.026	.81
25	359	0.004	> 100
	360	0.0025	30
30	361	0.005	> 20
	362	0.076	123
	363	0.0078	> 10
35	364	0.0069	> 20
	365	0.0074	45
40	366	0.013	45
	372	0.012	> 20
	472	0.041	245
45	474	0.0064	> 500
	485	4.7	83
	496	0.012	106
50	497	0.014	> 100
	512	0.0027	> 20

5	Compound No.	50% inhibitory concentration of HIV infection ( $\mu$ M)	50% cytotoxic concentration to MT-4 cells ( $\mu$ M)
10	513	0.0068	> 20
15	574	0.10	223
20	575	0.095	46
25	675	0.34	143
30	676	0.22	> 100
	685	3.8	> 100
	686	1.6	223
	689	0.45	17
	690	0.35	> 100
	704	0.012	20
	748	0.096	38
	749	0.091	> 20

35 **Claims**

1. A 6-substituted acyclopyrimidine nucleoside derivative represented by the following general formula I;

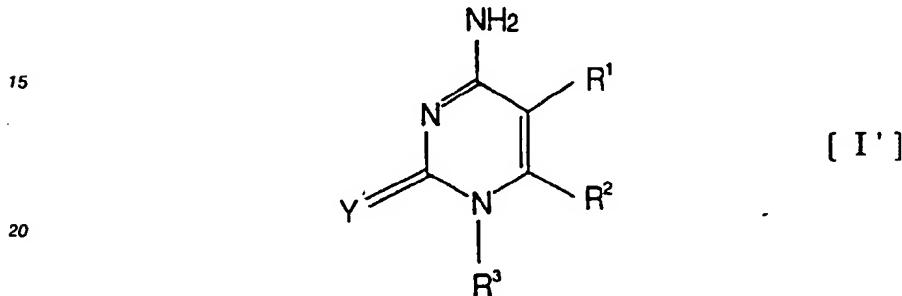


50 wherein R<sup>1</sup> represents a hydrogen atom, halogen atom, alkyl, cycloalkyl, alkenyl, alkynyl, alkylcarbonyl, arylcarbonyl, arylcarbonylalkyl, arylthio or aralkyl group; R<sup>2</sup> represents an arylthio, alkylthio, cycloalkylthio, arylsulfinyl, alkylsulfinyl, cycloalkylsulfinyl, alkenyl, alkynyl, aralkyl, arylcarbonyl, arylcarbonylalkyl or aryloxy group, those groups optionally substituted by one or more of substituents selected from a halogen atom, alkyl, halogenated alkyl, alkoxy, hydroxyl, nitro, amino, cyano and acyl groups; R<sup>3</sup> represents a hydrogen atom, methyl, branched alkyl or -CH<sub>2</sub>-Z-(CH<sub>2</sub>)<sub>n</sub>-R<sup>5</sup> group where R<sup>5</sup> represents a

hydrogen atom, halogen atom, hydroxyl, heterocyclic carbonyloxy, formyloxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, aralkylcarbonyloxy, arylcarbonyloxy, azido, alkoxy carbonyloxy, N-alkylcarbamoyloxy, N-arylcarbamoyloxy, N-alkylthiocarbamoyloxy, N-arylthiocarbamoyloxy, alkoxy, aralkyloxy, branched alkyl, cycloalkyl or aryl group, the alkoxy carbonyloxy to aryl groups mentioned above as R<sup>5</sup> optionally substituted

- 5 by one or more substituents selected from a halogen atom, aryl, alkyl, alkoxy and halogenated alkyl groups. Z represents an oxygen, sulfur atom or methylene group, and n represents 0 or an integer of 1 to 5. R<sup>4</sup> represents a hydrogen atom, alkyl or aralkyl group. X and Y represent an oxygen or sulfur atom independently, provided that when R<sup>4</sup> and Z represent a hydrogen atom and oxygen atom respectively R<sup>5</sup> does not represent a hydroxyl group, or a pharmaceutically acceptable salt thereof.

10 2. A 6-substituted acyclopyrimidine nucleoside derivative represented by the following general formula I':



25 wherein R<sup>1</sup> represents a hydrogen atom, halogen atom, alkyl, cycloalkyl, alkenyl, alkynyl, alkylcarbonyl, arylcarbonyl, arylcarbonylalkyl, arylthio or aralkyl group;

R<sup>2</sup> represents an arylthio, alkylthio, cycloalkylthio, arylsulfinyl, alkylsulfinyl, cycloalkylsulfinyl, alkenyl, alkynyl, aralkyl, arylcarbonyl, arylcarbonylalkyl or aryloxy group, those groups optionally substituted by one or more of substituents selected from a halogen atom, alkyl, halogenated alkyl, alkoxy, hydroxyl, nitro, amino, cyano and acyl groups;

30 R<sup>3</sup> represents a hydrogen atom, methyl, branched alkyl or -CH<sub>2</sub>-Z-(CH<sub>2</sub>)<sub>n</sub>-R<sup>5</sup> group where R<sup>5</sup> represents a hydrogen atom, halogen atom, hydroxyl, heterocyclic carbonyloxy, formyloxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, aralkylcarbonyloxy, arylcarbonyloxy, azido, alkoxy carbonyloxy, N-alkylcarbamoyloxy, N-arylcarbamoyloxy, N-alkylthiocarbamoyloxy, N-arylthiocarbamoyloxy, alkoxy, aralkyloxy, branched alkyl, cycloalkyl or aryl group, the alkoxy carbonyloxy to aryl groups mentioned above as R<sup>5</sup> optionally substituted

35 by one or more substituents selected from a halogen atom, aryl, alkyl, alkoxy and halogenated alkyl groups. Z represents an oxygen, sulfur atom or methylene group, and n represents 0 or an integer of 1 to 5.

Y represents an oxygen or sulfur atom,

or a pharmaceutically acceptable salt thereof.

40 3. A compound according to claim 1 or 2, wherein:

R<sup>1</sup> represents a hydrogen atom; halogen atom; C<sub>1</sub> to C<sub>10</sub> alkyl; C<sub>3</sub> to C<sub>10</sub> cycloalkyl; C<sub>2</sub> to C<sub>5</sub> alkenyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, cyano, C<sub>2</sub> to C<sub>6</sub> alkoxy carbonyl, carbamoyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, amino and nitro groups; C<sub>2</sub> to C<sub>5</sub> alkynyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, cyano, C<sub>2</sub> to C<sub>6</sub> alkoxy carbonyl, carbamoyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, amino and nitro groups; C<sub>2</sub> to C<sub>5</sub> alkylcarbonyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, cyano, C<sub>2</sub> to C<sub>6</sub> alkoxy carbonyl, carbamoyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, amino and nitro groups; C<sub>7</sub> to C<sub>13</sub> arylcarbonyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, cyano, C<sub>2</sub> to C<sub>6</sub> alkoxy carbonyl, carbamoyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, amino and nitro groups; or C<sub>7</sub> to C<sub>17</sub> aralkyl group optionally substituted by one or more substituents selected from a halogen atom, C<sub>5</sub> to C<sub>12</sub> aryl, cyano, C<sub>2</sub> to C<sub>6</sub> alkoxy carbonyl, carbamoyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, amino and nitro groups;

45 C<sub>8</sub> to C<sub>14</sub> arylcarbonylalkyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, cyano, C<sub>2</sub> to C<sub>6</sub> alkoxy carbonyl, carbamoyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, amino and nitro groups; C<sub>7</sub> to C<sub>13</sub> arylcarbonyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, cyano, C<sub>2</sub> to C<sub>6</sub> alkoxy carbonyl, carbamoyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, amino and nitro groups; or C<sub>7</sub> to C<sub>17</sub> aralkyl group optionally substituted by one or more substituents selected from a halogen atom, C<sub>5</sub> to C<sub>12</sub> aryl, cyano, C<sub>2</sub> to C<sub>6</sub> alkoxy carbonyl, carbamoyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, amino and nitro groups,

50 C<sub>8</sub> to C<sub>14</sub> arylcarbonylalkyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> arylthio optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; C<sub>1</sub> to C<sub>10</sub> alkylthio optionally substituted by one or more substituents

55 C<sub>8</sub> to C<sub>14</sub> arylthio optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; C<sub>1</sub> to C<sub>10</sub> alkylthio optionally substituted by one or more substituents

selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; C<sub>3</sub> to C<sub>10</sub> cycloalkylthio optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; C<sub>6</sub> to C<sub>12</sub> arylsulfinyl 5 optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; C<sub>1</sub> to C<sub>10</sub> alkylsulfinyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; C<sub>3</sub> to C<sub>10</sub> cycloalkylsulfinyl optionally substituted by one or more substituents 10 selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; C<sub>2</sub> to C<sub>5</sub> alkenyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; C<sub>7</sub> to C<sub>17</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; C<sub>7</sub> to C<sub>13</sub> arylcarbonyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; C<sub>8</sub> to C<sub>14</sub> arylcarbonylalkyl optionally substituted by one or more 20 substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; or C<sub>6</sub> to C<sub>12</sub> aryloxy group optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups. 25 R<sup>3</sup> represents a hydrogen atom; methyl; C<sub>3</sub> to C<sub>10</sub> branched alkyl; or -CH<sub>2</sub>-Z-(CH<sub>2</sub>)<sub>n</sub>-R<sup>5</sup> group where R<sup>5</sup> represents a hydrogen atom, halogen atom, hydroxyl, 5- or 6-membered heterocyclic carbonyloxy, formyloxy, C<sub>2</sub> to C<sub>11</sub> alkylcarbonyloxy, C<sub>4</sub> to C<sub>11</sub> cycloalkylcarbonyloxy, C<sub>8</sub> to C<sub>12</sub> aralkylcarbonyloxy, C<sub>7</sub> to C<sub>13</sub> arylcarbonyloxy, azido, C<sub>2</sub> to C<sub>1</sub> alkoxy carbonyloxy optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated 30 alkyl groups, C<sub>2</sub> to C<sub>11</sub> N-alkylcarbamoyloxy optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated alkyl groups, C<sub>7</sub> to C<sub>13</sub> N-aryliothiocarbamoyloxy optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated alkyl groups, C<sub>1</sub> to C<sub>10</sub> alkoxy 35 optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated alkyl groups, C<sub>7</sub> to C<sub>13</sub> aralkyloxy optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl groups, C<sub>3</sub> to C<sub>10</sub> branched alkyl optionally substituted by one or more 40 substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated alkyl groups, C<sub>3</sub> to C<sub>10</sub> cycloalkyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated alkyl 45 groups, or C<sub>6</sub> to C<sub>12</sub> aryl group optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated alkyl groups, Z represents an oxygen, sulfur atom or methylene group, and n represents 0 or an integer of 1 to 5, R<sup>4</sup> represents a hydrogen atom, C<sub>1</sub> to C<sub>13</sub> alkyl or C<sub>7</sub> to C<sub>13</sub> aralkyl group; and 50 X and Y independently represent an oxygen or sulfur atom; provided that when R<sup>4</sup> and Z represent a hydrogen atom and oxygen atom respectively R<sup>5</sup> does not represent hydroxyl group.

4. A compound according to claim 3, wherein:

R<sup>1</sup> represents a hydrogen atom; halogen atom; C<sub>1</sub> to C<sub>5</sub> alkyl; C<sub>3</sub> to C<sub>8</sub> cycloalkyl; C<sub>2</sub> to C<sub>5</sub> alkenyl 55 optionally substituted by one or more substituents selected from a halogen atom, phenyl, cyano, C<sub>2</sub> to C<sub>6</sub> alkoxy carbonyl and carbamoyl groups; C<sub>2</sub> to C<sub>5</sub> alkynyl optionally substituted by one or more substituents selected from a halogen atom, phenyl, cyano, C<sub>2</sub> to C<sub>6</sub> alkoxy carbonyl and carbamoyl groups; C<sub>2</sub> to C<sub>5</sub> alkyl carbonyl optionally substituted by one or more substituents selected from a halogen atom, phenyl, cyano, C<sub>2</sub> to C<sub>6</sub> alkoxy carbonyl and carbamoyl groups; C<sub>7</sub> to C<sub>13</sub> aryl carbonyl optionally substituted by one or more substituents selected from a halogen atom, phenyl, cyano, C<sub>2</sub> to C<sub>6</sub> alkoxy carbonyl and carbamoyl

groups;  $C_8$  to  $C_{14}$  arylcarbonylalkyl optionally substituted by one or more substituents selected from a halogen atom, phenyl, cyano,  $C_2$  to  $C_6$  alkoxy carbonyl and carbamoyl groups;  $C_6$  to  $C_{12}$  arylthio optionally substituted by one or more substituents selected from a halogen atom, phenyl, cyano,  $C_2$  to  $C_6$  alkoxy carbonyl and carbamoyl groups; or  $C_7$  to  $C_{17}$  aralkyl group optionally substituted by one or more substituents selected from a halogen atom, phenyl, cyano,  $C_2$  to  $C_6$  alkoxy carbonyl and carbamoyl groups,

5  $R^2$  represents  $C_6$  to  $C_{10}$  arylthio optionally substituted by one or more substituents selected from a halogen atom,  $C_1$  to  $C_5$  alkyl,  $C_1$  to  $C_5$  halogenated alkyl,  $C_1$  to  $C_5$  alkoxy, phenyl, hydroxyl, nitro, amino, cyano and  $C_2$  to  $C_7$  acyl groups;  $C_1$  to  $C_5$  alkylthio optionally substituted by one or more substituents selected from a halogen atom,  $C_1$  to  $C_5$  alkyl,  $C_1$  to  $C_5$  halogenated alkyl,  $C_1$  to  $C_5$  alkoxy, phenyl, hydroxyl, nitro, amino, cyano and  $C_2$  to  $C_7$  acyl groups;  $C_3$  to  $C_{10}$  cycloalkylthio optionally substituted by one or more substituents selected from a halogen atom,  $C_1$  to  $C_5$  alkyl,  $C_1$  to  $C_5$  halogenated alkyl,  $C_1$  to  $C_5$  alkoxy, phenyl, hydroxyl, nitro, amino, cyano and  $C_2$  to  $C_7$  acyl groups;  $C_6$  to  $C_{12}$  arylsulfinyl optionally substituted by one or more substituents selected from a halogen atom,  $C_1$  to  $C_5$  alkyl,  $C_1$  to  $C_5$  halogenated alkyl,  $C_1$  to  $C_5$  alkoxy, phenyl, hydroxyl, nitro, amino, cyano and  $C_2$  to  $C_7$  acyl groups;  $C_1$  to  $C_5$  alkylsulfinyl optionally substituted by one or more substituents selected from a halogen atom,  $C_1$  to  $C_5$  alkyl,  $C_1$  to  $C_5$  halogenated alkyl,  $C_1$  to  $C_5$  alkoxy, phenyl, hydroxyl, nitro, amino, cyano and  $C_2$  to  $C_7$  acyl groups;  $C_3$  to  $C_{10}$  cycloalkylsulfinyl optionally substituted by one or more substituents selected from a halogen atom,  $C_1$  to  $C_5$  alkyl,  $C_1$  to  $C_5$  halogenated alkyl,  $C_1$  to  $C_5$  alkoxy, phenyl, hydroxyl, nitro, amino, cyano and  $C_2$  to  $C_7$  acyl groups;  $C_2$  to  $C_5$  alkenyl optionally substituted by one or more substituents selected from a halogen atom,  $C_1$  to  $C_5$  alkyl,  $C_1$  to  $C_5$  halogenated alkyl,  $C_1$  to  $C_5$  alkoxy, phenyl, hydroxyl, nitro, amino, cyano and  $C_2$  to  $C_7$  acyl groups;  $C_1$  to  $C_5$  alkynyl optionally substituted by one or more substituents selected from a halogen atom,  $C_1$  to  $C_5$  alkyl,  $C_1$  to  $C_5$  halogenated alkyl,  $C_1$  to  $C_5$  alkoxy, phenyl, hydroxyl, nitro, amino, cyano and  $C_2$  to  $C_7$  acyl groups;  $C_7$  to  $C_{11}$  aralkyl optionally substituted by one or more substituents selected from a halogen atom,  $C_1$  to  $C_5$  alkyl,  $C_1$  to  $C_5$  halogenated alkyl,  $C_1$  to  $C_5$  alkoxy, phenyl, hydroxyl, nitro, amino, cyano and  $C_2$  to  $C_7$  acyl groups;  $C_7$  to  $C_{13}$  arylcarbonyl optionally substituted by one or more substituents selected from a halogen atom,  $C_1$  to  $C_5$  alkyl,  $C_1$  to  $C_5$  halogenated alkyl,  $C_1$  to  $C_5$  alkoxy, phenyl, hydroxyl, nitro, amino, cyano and  $C_2$  to  $C_7$  acyl groups;  $C_8$  to  $C_{14}$  arylcarbonylalkyl optionally substituted by one or more substituents selected from a halogen atom,  $C_1$  to  $C_5$  alkyl,  $C_1$  to  $C_5$  halogenated alkyl,  $C_1$  to  $C_5$  alkoxy, phenyl, hydroxyl, nitro, amino, cyano and  $C_2$  to  $C_7$  acyl groups; or  $C_6$  to  $C_{12}$  aryloxy group optionally substituted by one or more substituents selected from a halogen atom,  $C_1$  to  $C_5$  alkyl,  $C_1$  to  $C_5$  halogenated alkyl,  $C_1$  to  $C_5$  alkoxy, phenyl, hydroxyl, nitro, amino, cyano and  $C_2$  to  $C_7$  acyl groups.

5. A compound according to claim 4, wherein:

14  $R^1$  represents a hydrogen atom; halogen atom;  $C_1$  to  $C_5$  alkyl;  $C_3$  to  $C_8$  cycloalkyl;  $C_2$  to  $C_5$  alkenyl optionally substituted by one or more substituents selected from a halogen atom, phenyl, cyano,  $C_2$  to  $C_6$  alkoxy carbonyl and carbamoyl groups;  $C_2$  to  $C_5$  alkynyl optionally substituted by one or more substituents selected from a halogen atom, phenyl, cyano,  $C_2$  to  $C_6$  alkoxy carbonyl and carbamoyl groups;  $C_2$  to  $C_5$  alkylcarbonyl;  $C_7$  to  $C_{13}$  arylcarbonyl;  $C_8$  to  $C_{14}$  arylcarbonylalkyl;  $C_6$  to  $C_{12}$  arylthio; or  $C_7$  to  $C_{17}$  aralkyl group.

15  $R^2$  represents  $C_6$  to  $C_{10}$  arylthio optionally substituted by one or more substituents selected from a halogen atom,  $C_1$  to  $C_5$  alkyl,  $C_1$  to  $C_5$  halogenated alkyl,  $C_1$  to  $C_5$  alkoxy, phenyl, hydroxyl, nitro, amino, cyano and  $C_2$  to  $C_7$  acyl groups;  $C_1$  to  $C_5$  alkylthio;  $C_3$  to  $C_{10}$  cycloalkylthio optionally substituted by one or more substituents selected from a halogen atom,  $C_1$  to  $C_5$  alkyl,  $C_1$  to  $C_5$  halogenated alkyl,  $C_1$  to  $C_5$  alkoxy, phenyl, hydroxyl, nitro, amino, cyano and  $C_2$  to  $C_7$  acyl groups;  $C_6$  to  $C_{12}$  arylsulfinyl;  $C_1$  to  $C_5$  alkylsulfinyl;  $C_3$  to  $C_{10}$  cycloalkylsulfinyl;  $C_2$  to  $C_5$  alkenyl;  $C_2$  to  $C_5$  alkynyl;  $C_7$  to  $C_{11}$  aralkyl optionally substituted by one or more substituents selected from a halogen atom,  $C_1$  to  $C_5$  alkyl,  $C_1$  to  $C_5$  halogenated alkyl,  $C_1$  to  $C_5$  alkoxy, phenyl, hydroxyl, nitro, amino, cyano and  $C_2$  to  $C_7$  acyl groups;  $C_7$  to  $C_{13}$  arylcarbonyl;  $C_8$  to  $C_{14}$  arylcarbonylalkyl; or  $C_6$  to  $C_{12}$  aryloxy group, optionally substituted by one or more substituents selected from a halogen atom,  $C_1$  to  $C_5$  alkyl,  $C_1$  to  $C_5$  halogenated alkyl,  $C_1$  to  $C_5$  alkoxy, phenyl, hydroxyl, nitro, amino, cyano and  $C_2$  to  $C_7$  acyl groups.

16  $R^3$  represents a hydrogen atom; methyl; or  $-CH_2-Z-(CH_2)_n-R^5$  group where  $R^5$  represents a hydrogen atom, halogen atom, hydroxyl, 5- or 6-membered heterocyclic carbonyloxy, formyloxy,  $C_2$  to  $C_{11}$  alkylcarbonyloxy,  $C_4$  to  $C_{11}$  cycloalkylcarbonyloxy,  $C_8$  to  $C_{12}$  aralkylcarbonyloxy,  $C_7$  to  $C_{13}$  arylcarbonyloxy, azido,  $C_2$  to  $C_{11}$  alkoxy carbonyloxy,  $C_2$  to  $C_8$  N-alkyl carbamoyloxy,  $C_7$  to  $C_{13}$  N-aryl carbamoyloxy optionally substituted by one or more substituents selected from a halogen atom,  $C_6$  to  $C_{12}$  aryl,  $C_1$  to  $C_5$  alkyl,  $C_1$  to  $C_5$  alkoxy and  $C_1$  to  $C_5$  halogenated alkyl groups,  $C_2$  to  $C_8$  N-alkylthiocarbamoyloxy,  $C_7$  to  $C_{13}$  N-arylthiocarbamoyloxy optionally substituted by one or more substituents selected from a halogen atom,  $C_6$  to  $C_{12}$  aryl,  $C_1$  to  $C_5$  alkyl,  $C_1$  to  $C_5$  alkoxy and  $C_1$  to  $C_5$  halogenated alkyl groups,  $C_3$  to  $C_5$  branched alkyl,  $C_5$  to  $C_7$  cycloalkyl, or  $C_6$  to  $C_{10}$  aryl group optionally substituted by one or more substituents selected from a halogen atom, phenyl, cyano,  $C_2$  to  $C_6$  alkoxy carbonyl and carbamoyl groups;  $C_2$  to  $C_5$  alkynyl;  $C_7$  to  $C_{11}$  aralkyl;  $C_8$  to  $C_{14}$  arylcarbonylalkyl;  $C_6$  to  $C_{12}$  arylthio; or  $C_7$  to  $C_{17}$  aralkyl group.

halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated alkyl groups, Z represents an oxygen, sulfur atom or methylene group, and n represents 0 or an integer of 1 to 5.

6. A compound according to claim 5, wherein:

R<sup>1</sup> represents a hydrogen atom; halogen atom; C<sub>1</sub> to C<sub>5</sub> alkyl; C<sub>3</sub> to C<sub>8</sub> cycloalkyl; or C<sub>2</sub> to C<sub>5</sub> alkenyl optionally substituted by one or more substituents selected from a halogen atom, phenyl, cyano, C<sub>2</sub> to C<sub>6</sub> alkoxy carbonyl and carbamoyl groups.

R<sup>2</sup> represents C<sub>6</sub> to C<sub>10</sub> arylthio optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, phenyl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; C<sub>3</sub> to C<sub>10</sub> cycloalkylthio optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, phenyl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; or C<sub>7</sub> to C<sub>11</sub> aralkyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, phenyl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups.

R<sup>3</sup> represents a hydrogen atom; methyl; or -CH<sub>2</sub>-Z-(CH<sub>2</sub>)<sub>n</sub>-R<sup>5</sup> group where R<sup>5</sup> represents a hydrogen atom, halogen atom, hydroxyl, 5- or 6-membered heterocyclic carbonyloxy, formyloxy, C<sub>2</sub> to C<sub>11</sub> alkyl carbonyloxy, C<sub>4</sub> to C<sub>11</sub> cycloalkyl carbonyloxy, C<sub>8</sub> to C<sub>12</sub> aralkyl carbonyloxy, C<sub>7</sub> to C<sub>13</sub> aryl carbonyloxy, azido, C<sub>2</sub> to C<sub>11</sub> alkoxy carbonyloxy, C<sub>2</sub> to C<sub>8</sub> N-alkyl carbamoyloxy, C<sub>7</sub> to C<sub>13</sub> N-aryl carbamoyloxy, C<sub>2</sub> to C<sub>8</sub> N-alkyl thiocarbamoyloxy, C<sub>7</sub> to C<sub>13</sub> N-aryl thiocarbamoyloxy, C<sub>1</sub> to C<sub>10</sub> alkoxy, C<sub>7</sub> to C<sub>13</sub> aralkyl, C<sub>3</sub> to C<sub>5</sub> branched alkyl, C<sub>5</sub> to C<sub>7</sub> cycloalkyl, or C<sub>6</sub> to C<sub>10</sub> aryl group optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated alkyl groups, Z represents an oxygen, sulfur atom or methylene group, and n represents 0 or an integer of 1 to 5.

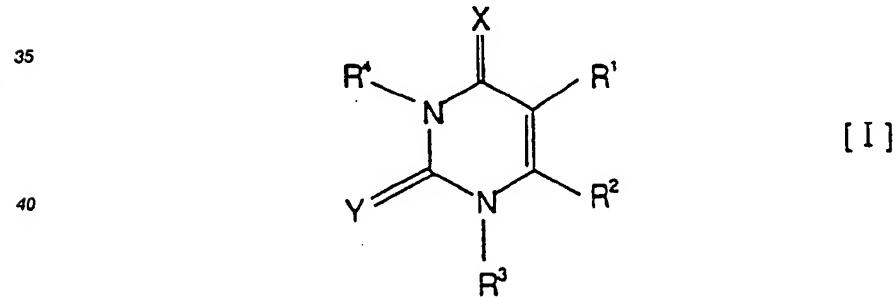
7. An antiviral agent containing as an active ingredient a 6-substituted acyclopyrimidine nucleoside derivative or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 6.

25 8. A pharmaceutical composition containing a derivative of any of claims 1 to 6 or a pharmaceutically acceptable salt thereof in association with a pharmaceutical vehicle.

9. The pharmaceutical composition of claim 9 which has effective antiviral activity, particularly anti-retroviral activity.

10. The use of a derivative of any of claims 1 to 6 or a pharmaceutically acceptable salt thereof in a process for the production of a pharmaceutical composition for the treatment or prevention of diseases caused by viral, particularly retroviral infection, especially in human beings.

30 11. A process for the preparation of a compound represented by the following general formula I;



wherein:

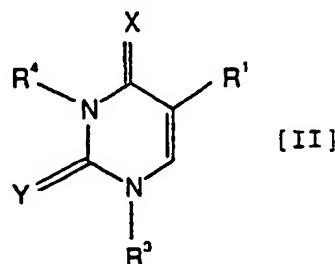
R<sup>1</sup> represents a hydrogen atom; halogen atom; C<sub>1</sub> to C<sub>10</sub> alkyl; C<sub>3</sub> to C<sub>10</sub> cycloalkyl; C<sub>2</sub> to C<sub>5</sub> alkenyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, cyano, C<sub>2</sub> to C<sub>6</sub> alkoxy carbonyl, carbamoyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, amino and nitro groups; C<sub>2</sub> to C<sub>5</sub> alkynyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl cyano, C<sub>2</sub> to C<sub>6</sub> alkoxy carbonyl, carbamoyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, amino and nitro groups; C<sub>2</sub> to C<sub>5</sub> alkyl carbonyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, cyano, C<sub>2</sub> to C<sub>6</sub> alkoxy carbonyl, carbamoyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, amino and nitro groups; C<sub>7</sub> to C<sub>13</sub> aryl carbonyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, cyano, C<sub>2</sub> to C<sub>6</sub> alkoxy carbonyl, carbamoyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, amino and nitro groups; C<sub>8</sub> to C<sub>14</sub> aryl carbonyl alkyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, cyano, C<sub>2</sub> to C<sub>6</sub> alkoxy carbonyl, carbamoyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, amino and nitro groups; C<sub>6</sub> to C<sub>12</sub> arylthio optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, cyano, C<sub>2</sub> to C<sub>6</sub>

alkoxycarbonyl, carbamoyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, amino and nitro groups; or C<sub>7</sub> to C<sub>17</sub> aralkyl group optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, cyano, C<sub>2</sub> to C<sub>6</sub> alkoxycarbonyl, carbamoyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, amino and nitro groups.

5 R<sup>2</sup> represents C<sub>6</sub> to C<sub>12</sub> arylthio optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; C<sub>1</sub> to C<sub>10</sub> alkylthio optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; C<sub>3</sub> to C<sub>10</sub> cycloalkylthio optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; C<sub>6</sub> to C<sub>12</sub> arylsulfinyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; C<sub>1</sub> to C<sub>10</sub> alkylsulfinyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; C<sub>3</sub> to C<sub>10</sub> cycloalkylsulfinyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; C<sub>2</sub> to C<sub>5</sub> alkynyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; C<sub>7</sub> to C<sub>17</sub> aralkyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; C<sub>7</sub> to C<sub>13</sub> arylcarbonyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; C<sub>8</sub> to C<sub>14</sub> arylcarbonylalkyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups; or C<sub>6</sub> to C<sub>12</sub> aryloxy group optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups,

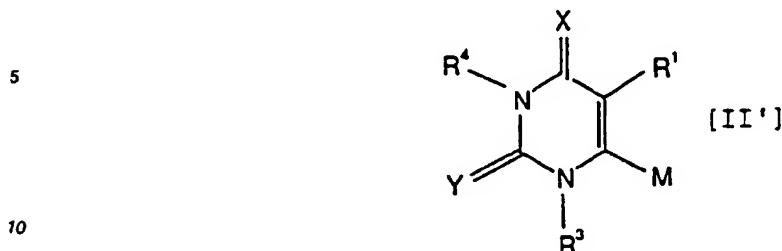
35 R<sup>3</sup> represents methyl; C<sub>3</sub> to C<sub>10</sub> branched alkyl; or -CH<sub>2</sub>-Z-(CH<sub>2</sub>)<sub>n</sub>-R<sup>5</sup> group where R<sup>5</sup> represents a hydrogen atom, halogen atom, azido, hydroxyl, C<sub>1</sub> to C<sub>10</sub> alkoxy optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated alkyl groups, C<sub>7</sub> to C<sub>13</sub> aralkyloxy optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated alkyl groups, C<sub>3</sub> to C<sub>10</sub> branched alkyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated alkyl groups, C<sub>3</sub> to C<sub>10</sub> cycloalkyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated alkyl groups, or C<sub>6</sub> to C<sub>12</sub> aryl group optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated alkyl groups, Z represents an oxygen, sulfur atom or methylene group, and n represents 0 or an integer of 1 to 5,

40 R<sup>4</sup> represents a hydrogen atom, C<sub>1</sub> to C<sub>13</sub> alkyl or C<sub>7</sub> to C<sub>13</sub> aralkyl group; and X and Y independently represent an oxygen or sulfur atom; provided that when R<sup>4</sup> and Z represent a hydrogen atom and oxygen atom respectively R<sup>5</sup> does not represent hydroxyl group, which comprises reacting a compound represented by the following general formula II;



wherein R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined above, with an organic alkali metal

compound to obtain a compound represented by the following general formula II' :



wherein R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined above and M represents an alkaline metal, and then reacting the obtained compound of the formula II' with a compound represented by the following general formula III;

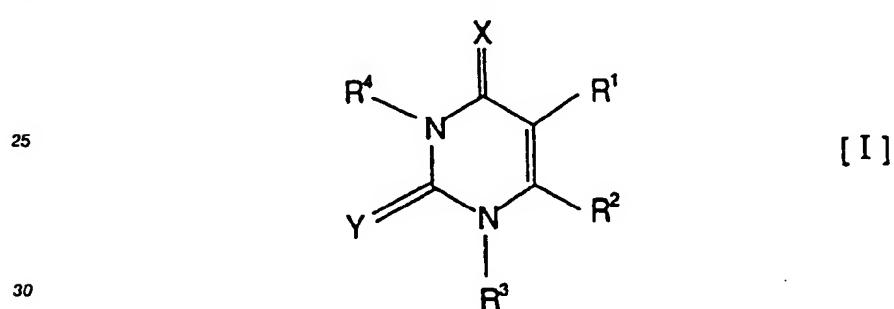
15

$R^2X'$  [III]

wherein R<sup>2</sup> has the same meaning as defined above and X' represents a halogen atom, arylthio or alkoxy group, to obtain the compound of the formula I above.

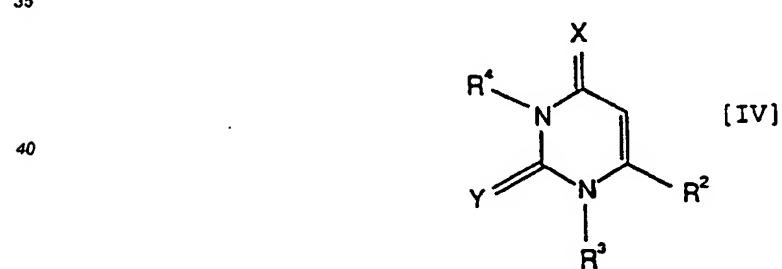
20

12. A process for the preparation of a compound represented by the following general formula I;

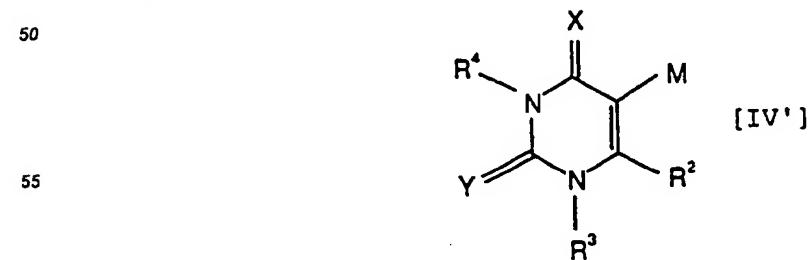


35

wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 1, which comprises reacting a compound represented by the following general formula IV;



wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 11, with an organic alkali metal compound to obtain a compound represented by the following general formula IV' ;

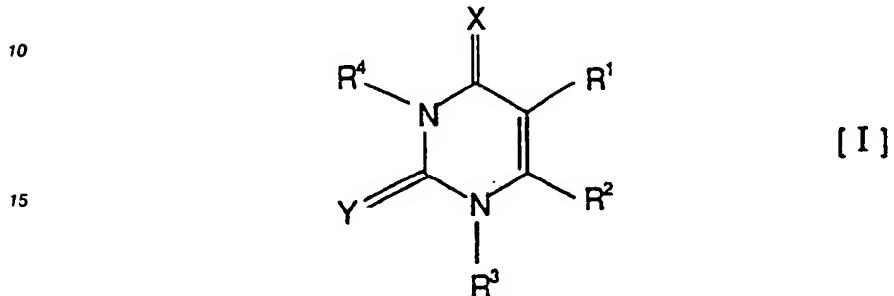


wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 11 and M represents an alkali metal, and then reacting the obtained compound of the formula IV with a compound represented by the following general formula V;

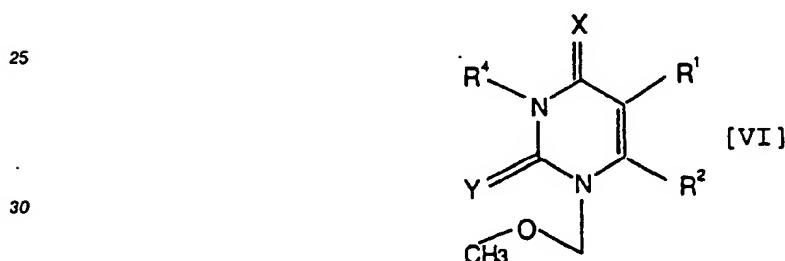
R<sup>1</sup>X<sup>2</sup> [V]

5 wherein R<sup>1</sup> has the same meaning as defined in claim 11 and X<sup>2</sup> represents a halogen atom, arylthio or alkoxy group, to obtain the compound of the formula I above.

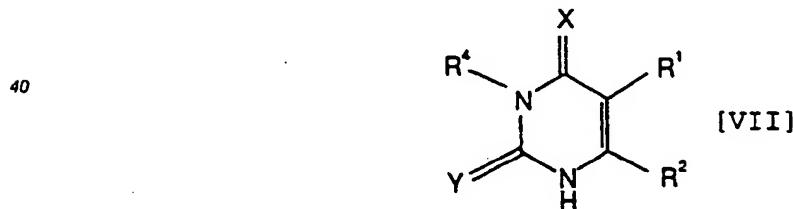
3. A process for the preparation of a compound represented by the following general formula I;



20 wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 11, which comprises reacting a compound represented by the following general formula VI;



35 wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 11, with an acid to obtain a compound represented by the following general formula VII;

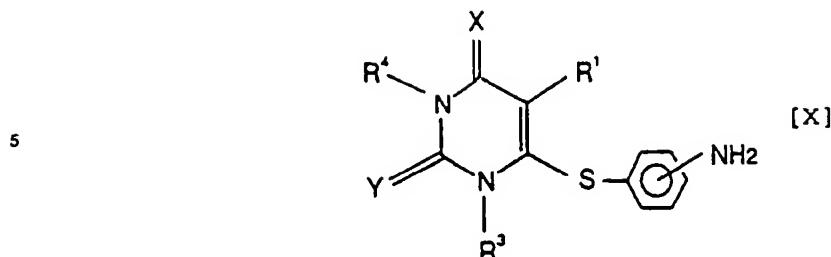


wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 11, and then reacting the obtained compound of the formula VII with a compound represented by the following general formula VIII;

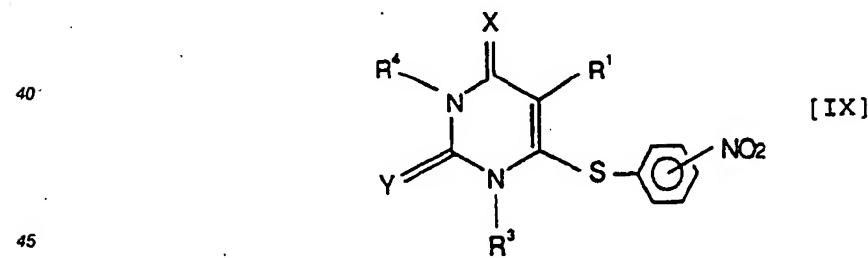
R<sup>3</sup>X<sup>3</sup> [VIII]

50 wherein R<sup>3</sup> has the same meaning as defined in claim 11 and X<sup>3</sup> represents a sulfonyloxy group, in the presence of a base to obtain the compound of the formula I above.

14. A process for the preparation of a compound represented by the following general formula X;

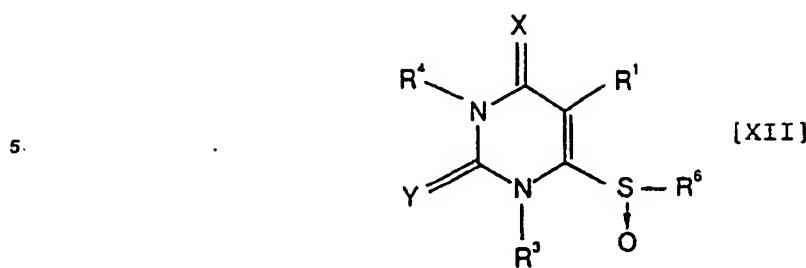


10 wherein R<sup>1</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 11 and R<sup>3</sup> represents a hydrogen atom; methyl; C<sub>3</sub> to C<sub>10</sub> branched alkyl; or -CH<sub>2</sub>-Z-(CH<sub>2</sub>)<sub>n</sub>-R<sup>5</sup> group where R<sup>5</sup> represents a hydrogen atom, halogen atom, hydroxyl, 5- or 6-membered heterocyclic carbonyloxy, formyloxy, C<sub>2</sub> to C<sub>11</sub> alkylcarbonyloxy, C<sub>4</sub> to C<sub>11</sub> cycloalkylcarbonyloxy, C<sub>8</sub> to C<sub>12</sub> aralkylcarbonyloxy, C<sub>7</sub> to C<sub>13</sub> arylcarbonyloxy, azido, 15 C<sub>2</sub> to C<sub>11</sub> alkoxy carbonyloxy optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated alkyl groups, C<sub>2</sub> to C<sub>11</sub> N-alkylcarbamoyloxy optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated alkyl groups, C<sub>7</sub> to C<sub>13</sub> N-arylcaramoyloxy optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to 20 C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated alkyl groups, C<sub>2</sub> to C<sub>11</sub> N-alkylthiocaramoyloxy optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated alkyl groups, C<sub>7</sub> to C<sub>13</sub> N-aryltiocaramoyloxy optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated alkyl groups, C<sub>1</sub> to C<sub>10</sub> alkoxy 25 optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated alkyl groups, C<sub>7</sub> to C<sub>13</sub> aralkyloxy optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated alkyl groups, C<sub>3</sub> to C<sub>10</sub> branched alkyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated alkyl groups, C<sub>3</sub> to C<sub>10</sub> cycloalkyl optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated alkyl groups, or C<sub>6</sub> to C<sub>12</sub> aryl group optionally substituted by one or more substituents selected from a halogen atom, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy and C<sub>1</sub> to C<sub>5</sub> halogenated alkyl groups, Z represents an oxygen, sulfur atom or methylene group, and n represents 0 or an integer of 1 to 5, which comprises 30 35 hydrogenating a compound represented by the following general formula IX:

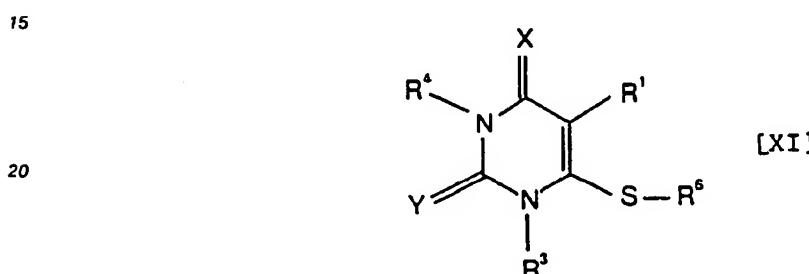


55 wherein R<sup>1</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 11 and R<sup>3</sup> has the same meaning as defined above, in the presence of a catalyst to obtain the compound of the formula X above.

50 15. A process for the preparation of a compound represented by the following general formula XII;

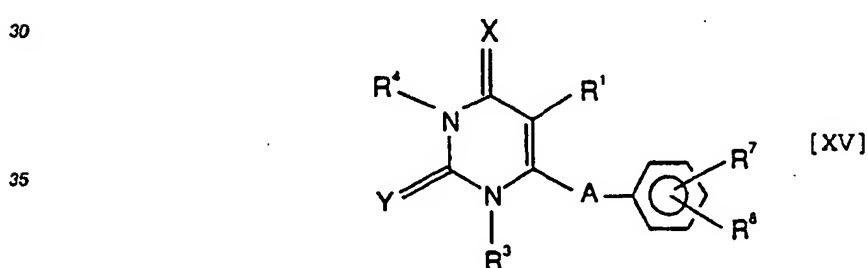


wherein R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 14 and R<sup>6</sup> represents C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>1</sub> to C<sub>10</sub> alkyl or C<sub>3</sub> to C<sub>10</sub> cycloalkyl group, which comprises converting a compound represented by the following general formula XI;

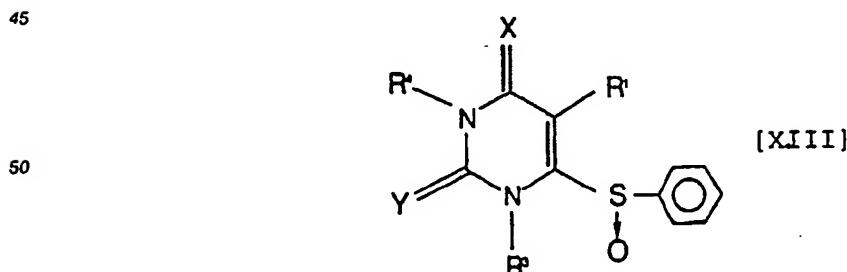


25 wherein R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 4 and R<sup>6</sup> has the same meaning as defined above into the compound of the formula XII above by an action of oxidizing agent.

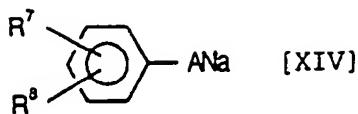
16. A process for the preparation of a compound represented by the following general formula XV;



40 wherein R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 14, R<sup>7</sup> and R<sup>8</sup> independently represent a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, hydroxyl, nitro, amino, cyano or C<sub>2</sub> to C<sub>7</sub> acyl group and A represents a sulfur or oxygen atom, which comprises reacting a compound represented by the following general formula XIII;



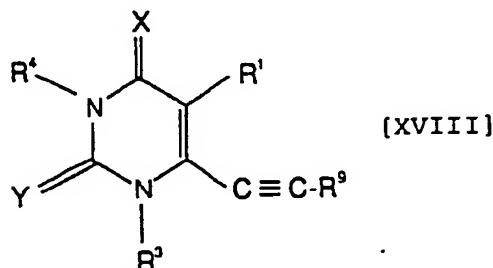
55 wherein R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 14, with a compound represented by the following general formula XIV;



wherein R<sup>7</sup> and R<sup>8</sup> have the same meanings as defined above, to obtain the compound of the formula XV above.

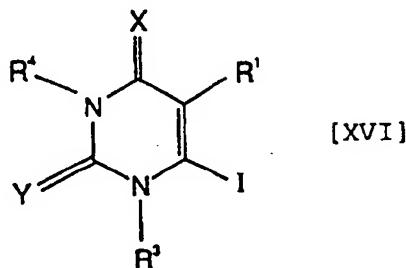
17. A process for the preparation of a compound represented by the following general formula XVIII;

10



wherein R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 14 and R<sup>9</sup> represents C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>6</sub> to C<sub>12</sub> aryl or silyl group, which comprises reacting a compound represented by the following general formula XVI;

25



wherein R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 14, with a compound represented by the following general formula XVII;

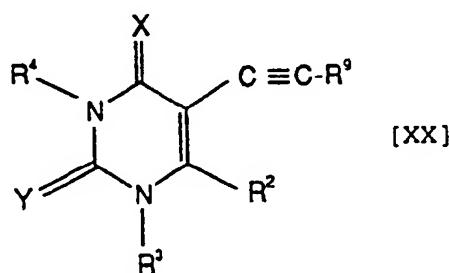
40

HC≡C-R<sup>9</sup> [XVII]

wherein R<sup>9</sup> has the same meaning as defined above, in the presence of a palladium catalyst to obtain the compound of the formula XVIII above.

18. A process for the preparation of a compound represented by the following general formula XX;

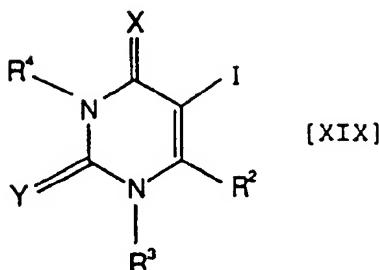
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55

wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 14 and R<sup>9</sup> represents C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>6</sub> to C<sub>12</sub> aryl or silyl group, which comprises reacting a compound represented by the following general formula XIX;

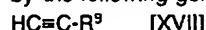
5



[XIX]

10

wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 14, with a compound represented by the following general formula XVII;

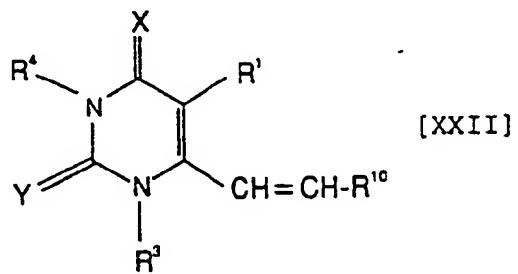


15

wherein R<sup>9</sup> has the same meaning as defined above, in the presence of a palladium catalyst to obtain the compound of the formula XX above.

19. A process for the preparation of a compound represented by the following general formula XXII;

20

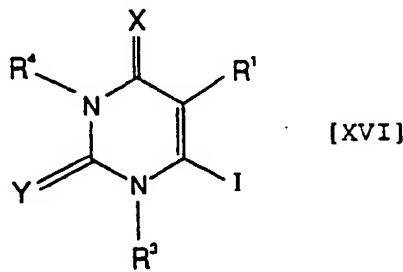


[XXII]

25

wherein R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 14 and R<sup>10</sup> represents C<sub>2</sub> to C<sub>6</sub> alkoxycarbonyl, nitrile or carbamoyl group, which comprises reacting a compound represented by the following general formula XVI;

35



[XVI]

40

wherein R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 14, with a compound represented by the following general formula XXI;

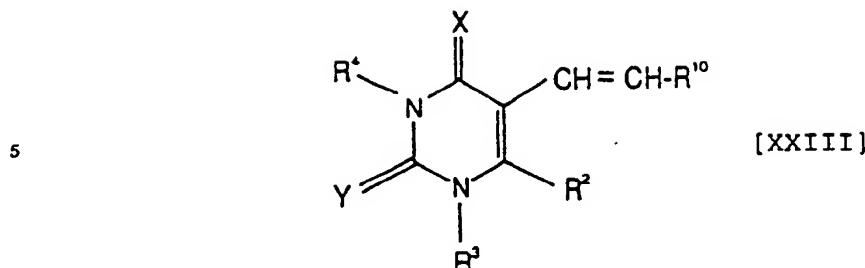


wherein R<sup>10</sup> has the same meaning, as defined above, in the presence of a palladium catalyst to obtain the compound of the formula XXII above.

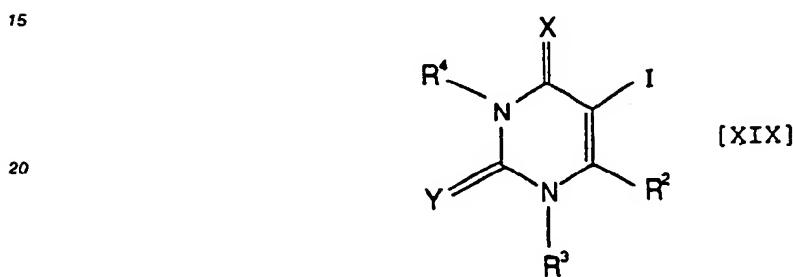
20. A process for the preparation of a compound represented by the following general formula XXIII;

50

55



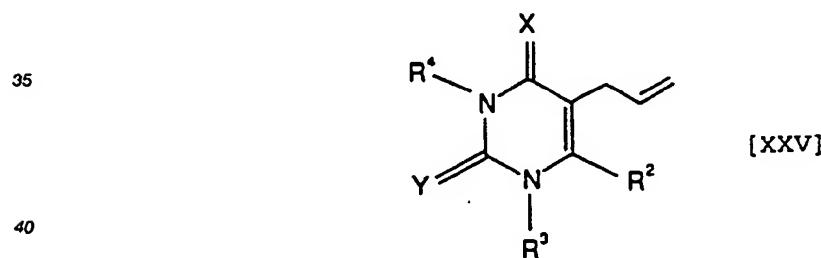
wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 14 and R<sup>10</sup> has the same meaning as defined in claim 19, which comprises reacting a compound represented by the following general formula XIX;



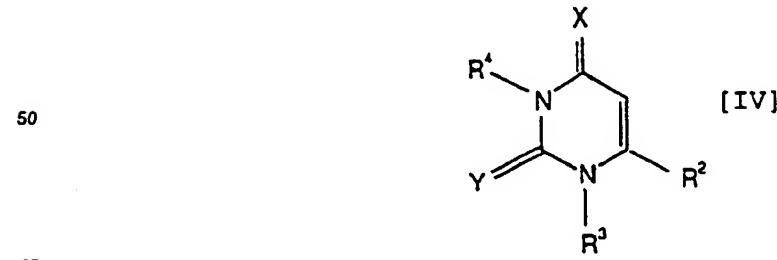
25 wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 14, with a compound represented by the following general formula XVII;

H<sub>2</sub>C=CH-R<sup>10</sup> [XXI]  
30 wherein R<sup>10</sup> has the same meaning as defined in claim 19, in the presence of a palladium catalyst to obtain the compound of the formula XXIII above.

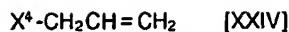
21. A process for the preparation of a compound represented by the following general formula XXV;



45 wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 14, which comprises reacting a compound represented by the following general formula IV;



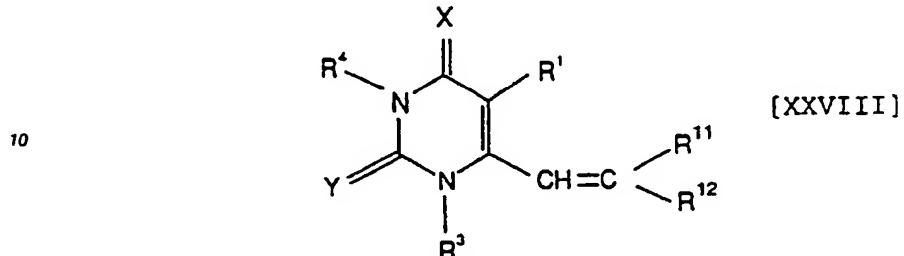
55 wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 14, with a compound represented by the following general formula XXIV;



wherein  $X^4$  represents a halogen atom, in the presence of a palladium catalyst to obtain the compound of the formula XXV above.

22. A process for the preparation of a compound represented by the following general formula XXVIII;

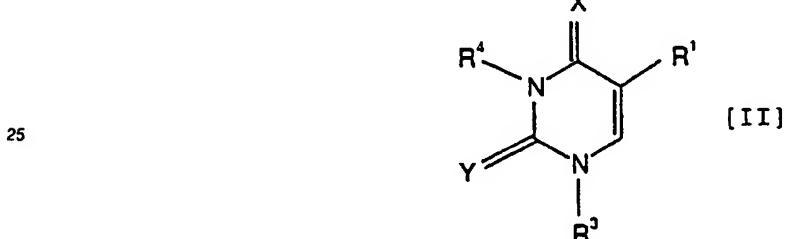
5



15

wherein R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 11, and R<sup>11</sup> and R<sup>12</sup> independently represent a hydrogen atom, C<sub>1</sub> to C<sub>3</sub> alkyl or C<sub>6</sub> to C<sub>12</sub> aryl group, which comprises reacting a compound represented by the following general formula II;

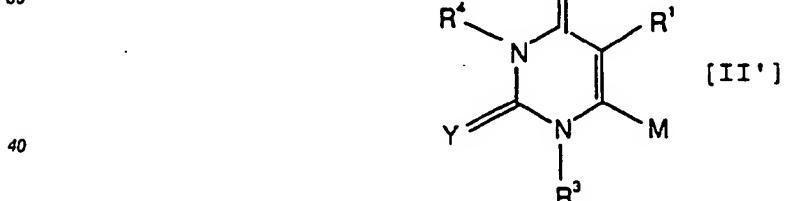
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30

wherein R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 11, with an organic alkali metal compound to obtain a compound represented by the following general formula II';

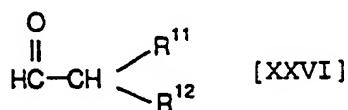
35



45

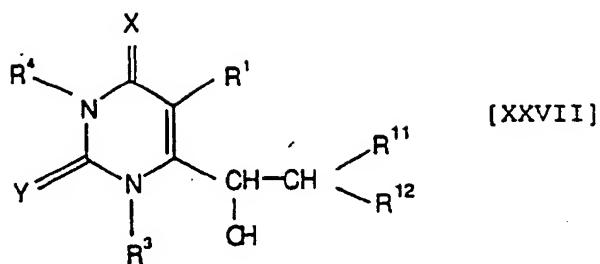
wherein R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 11 and M represents an alkali metal, reacting the obtained compound of the formula II' with a compound represented by the following general formula XXVI;

50



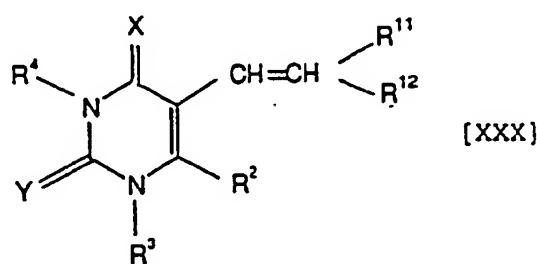
55

wherein R<sup>11</sup> and R<sup>12</sup> have the same meanings as defined above to obtain a compound represented by the following general formula XXVII;

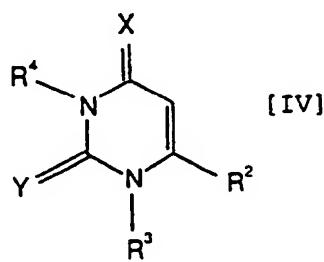


10 wherein R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 11 and R<sup>11</sup> and R<sup>12</sup> have the same meanings defined as above, and then dehydrating the obtained compound of the formula XXVII using a dehydrating agent to obtain the compound of the formula XXVIII above.

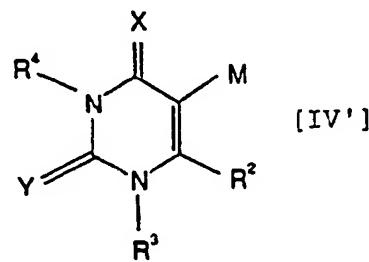
15 23. A process for the preparation of a compound represented by the following general formula XXX;



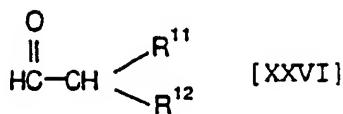
wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 14 and R<sup>11</sup> and R<sup>12</sup> independently represent a hydrogen atom, C<sub>1</sub> to C<sub>3</sub> alkyl or C<sub>6</sub> to C<sub>12</sub> aryl group, which comprises reacting a compound represented by the following general formula IV;



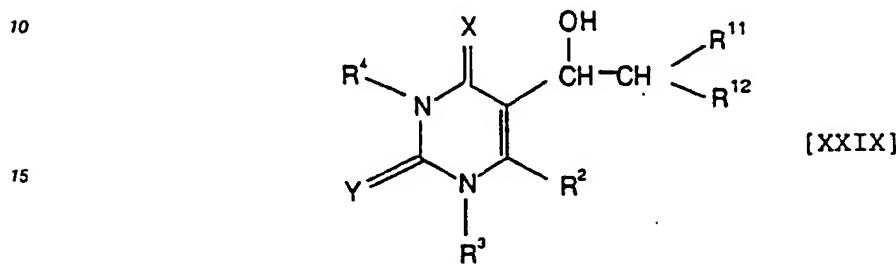
40 wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 14, with an organic alkali metal compound to obtain a compound represented by the following general formula IV';



55 wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 11 and M represents an alkali metal, reacting the obtained compound of the formula IV' with a compound represented by the following general formula XXVI;

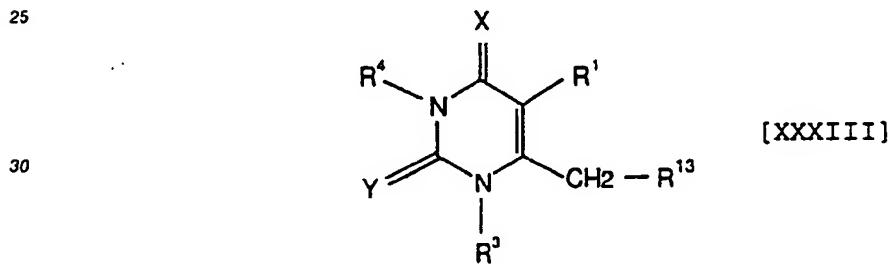


wherein R<sup>11</sup> and R<sup>12</sup> have the same meanings as defined above, to obtain a compound represented by the following general formula XXIX;

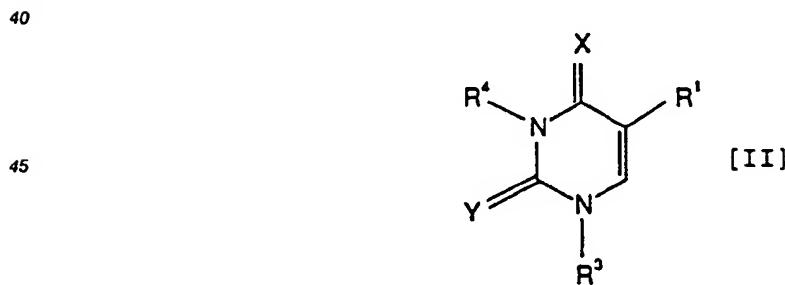


20 wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 14 and R<sup>11</sup> and R<sup>12</sup> have the same meanings as defined above, and then dehydrating the obtained compound of the formula XXIX using a dehydrating agent to obtain the compound of the formula XXX above.

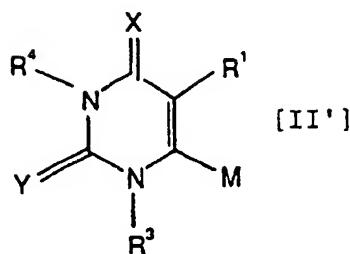
24. A process for the preparation of a compound represented by the following general formula XXXIII;



35 wherein R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 11 and R<sup>13</sup> represents C<sub>6</sub> to C<sub>12</sub> aryl group optionally substituted by one or more substituents selected from a halogen atom, C<sub>1</sub> to C<sub>5</sub> alkyl, C<sub>1</sub> to C<sub>5</sub> halogenated alkyl, C<sub>1</sub> to C<sub>5</sub> alkoxy, C<sub>6</sub> to C<sub>12</sub> aryl, hydroxyl, nitro, amino, cyano and C<sub>2</sub> to C<sub>7</sub> acyl groups, which comprises reacting a compound represented by the following general formula II;



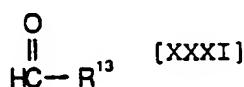
50 wherein R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y have the same meanings as defined in claim 11, with an organic alkali metal compound to obtain a compound represented by the following general formula II;



10

wherein R¹, R³, R⁴, X and Y have the same meanings as defined in claim 11 and M represents an alkali metal, reacting the obtained compound of the formula II' with a compound represented by the following general formula XXXI;

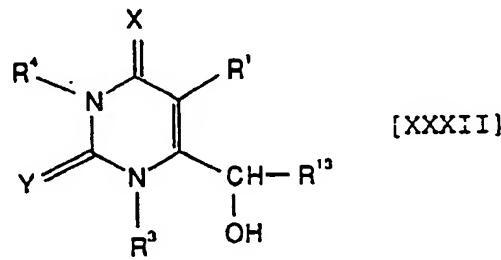
15



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wherein R¹³ has the same meaning as defined above to obtain a compound represented by the following general formula XXXII;

25

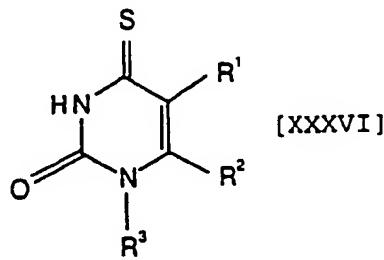


30

wherein R¹, R³, R⁴, X and Y have the same meanings as defined in claim 11 and R¹³ has the same meaning as defined above, and then reducing the obtained compound of the formula XXXII using a reducing agent to obtain the compound of the formula XXXIII above.

35 25. A process for the preparation of a compound represented by the following general formula XXXVI;

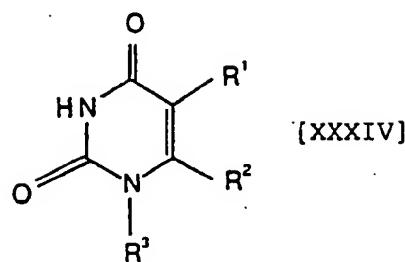
40



45

wherein R¹, R² and R³ have the same meanings as defined in claim 14, which comprises reacting a compound represented by the following general formula XXXIV;

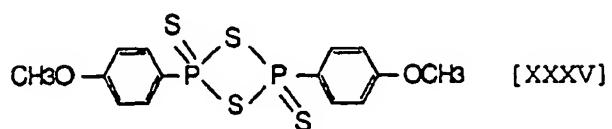
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10

wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> have the same meanings as defined in claim 14 with a compound represented by the following general formula XXXV;

15

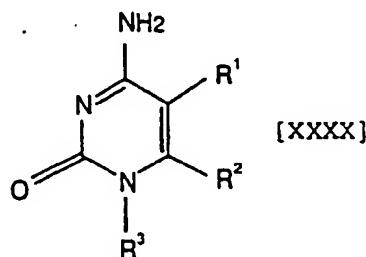


20

to obtain the compound of the formula XXXVI above.

26. A process for the preparation of a compound represented by the following general formula XXXX;

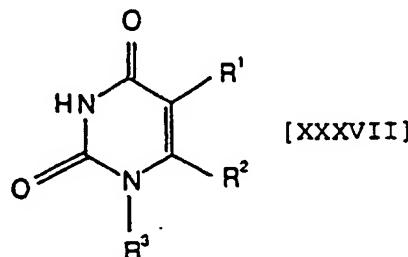
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30

35 wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> have the same meanings as defined in claim 14, which comprises represented by the following general formula XXXVII;

40

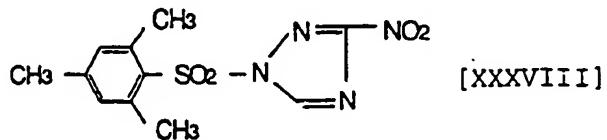


45

wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> have the same meanings as defined in claim 14, with a compound represented by the following general formula XXXVIII;

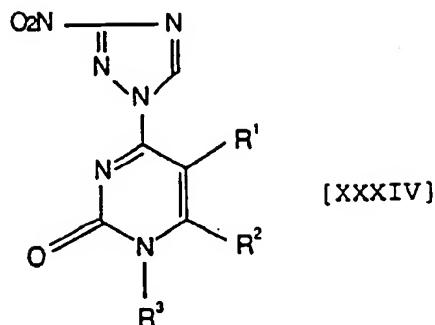
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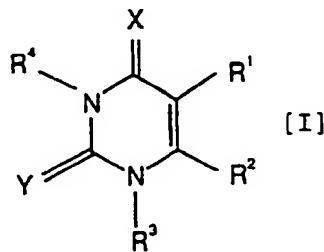
in a solvent in the presence of diphenylphosphonic acid to obtain a compound of the following general

formula XXXIV;

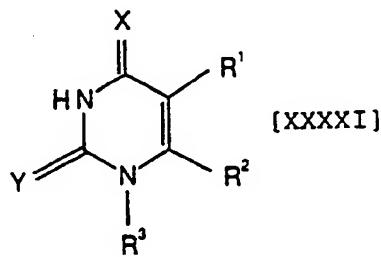


wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> have the same meanings as defined in claim 14, and reacting the obtained compound of the formula XXXIV with aqueous ammonia to obtain the compound of the formula XXXX above.

27. A process for the preparation of a compound represented by the following general formula I:



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, X and Y have the same meanings as defined in claim 14 and R<sup>4</sup> has the same meaning as defined in claim 11, which comprises reacting a compound represented by the following general formula XXXXI;

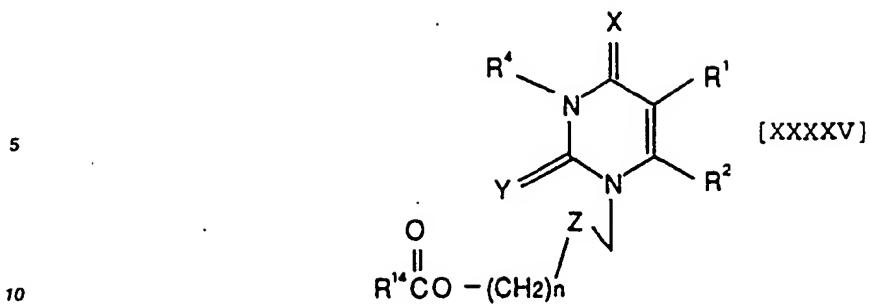


wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, X and Y have the same meanings as defined in claim 14 with a compound represented by the following general formula XXXXII;

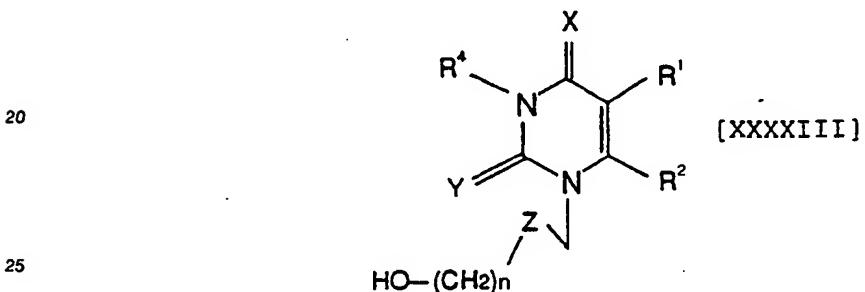
R<sup>4</sup>X<sup>5</sup> [XXXXII]

wherein R<sup>4</sup> have the same meanings as defined in claim 1 and X<sup>5</sup> represents a halogen atom or sulfonyloxy group, in the presence of a base to obtain the compound of the formula I above.

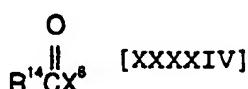
28. A process for the preparation of a compound represented by the following general formula XXXXV;



15 wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, X, Y, Z and n have the same meanings as defined in claim 11 and R<sup>14</sup> represents C<sub>1</sub> to C<sub>10</sub> alkyl, C<sub>3</sub> to C<sub>10</sub> cycloalkyl, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>7</sub> to C<sub>11</sub> aralkyl or 5- or 6-membered heterocyclic group, which comprises reacting a compound represented by the following general formula XXXXIII;

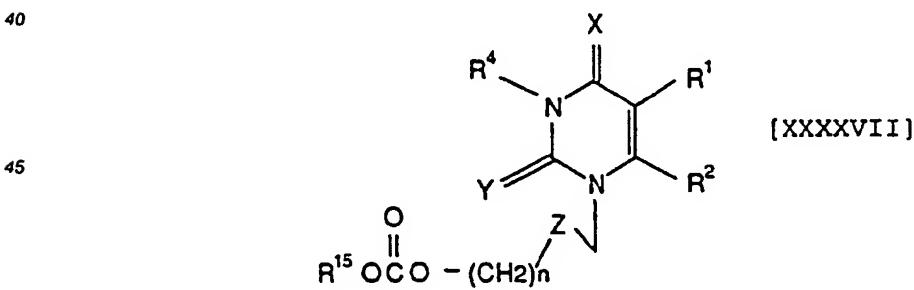


30 wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, X, Y, Z and n have the same meanings as defined in claim 11, with a compound represented by the following general formula XXXXIV;

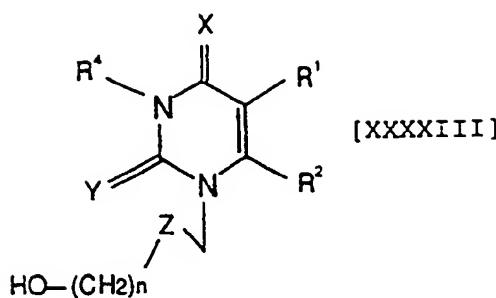


35 wherein R<sup>14</sup> has the same meaning as defined above and X<sup>6</sup> represents a halogen atom or -OCOR<sup>14</sup>, in a solvent in the presence of a base to obtain the compound of the formula XXXXV above.

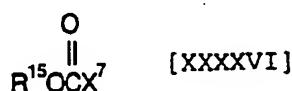
29. A process for the preparation of a compound represented by the following general formula XXXXVII;



50 wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, X, Y, Z and n have the same meanings as defined in claim 11 and R<sup>15</sup> represents C<sub>1</sub> to C<sub>10</sub> alkyl, which comprises reacting a compound represented by the following general formula XXXXIII;

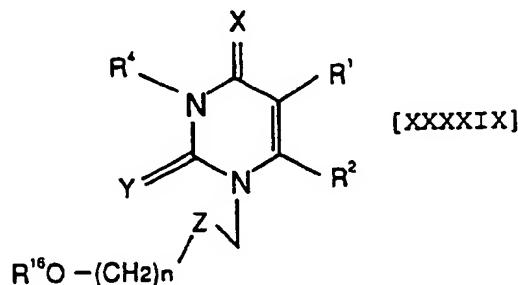


wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, X, Y, Z and n have the same meanings as defined in claim 11, with a compound represented by the following general formula XXXVI;

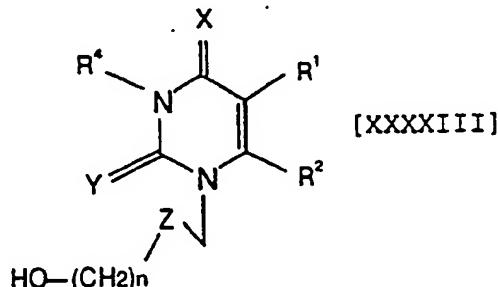


20 wherein R<sup>15</sup> has the same meaning as defined above and X<sup>7</sup> represents a halogen atom or -OCOOR<sup>15</sup>, in a solvent in the presence of a base to obtain the compound of the formula XXXVII above.

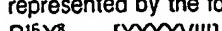
30 A process for the preparation of a compound represented by the following general formula XXXIX;



35 wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, X, Y, Z and n have the same meanings as defined in claim 11 and R<sup>16</sup> represents C<sub>1</sub> to C<sub>10</sub> alkyl, C<sub>7</sub> to C<sub>13</sub> aralkyl or formyl group, which comprises reacting a compound represented by the following general formula XXXIII;

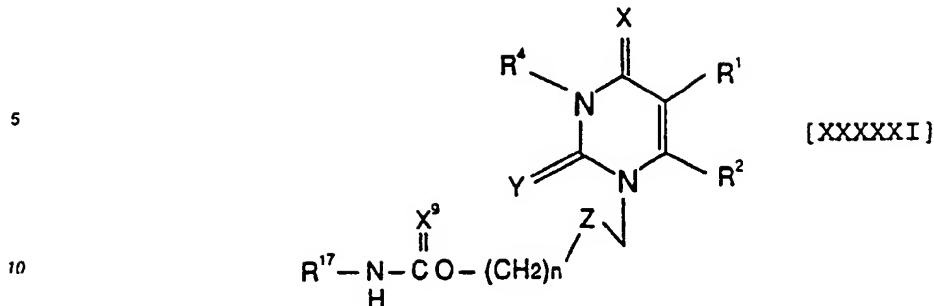


50 wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, X, Y, Z and n have the same meanings as defined in claim 11, with a compound represented by the following general formula XXXVIII;

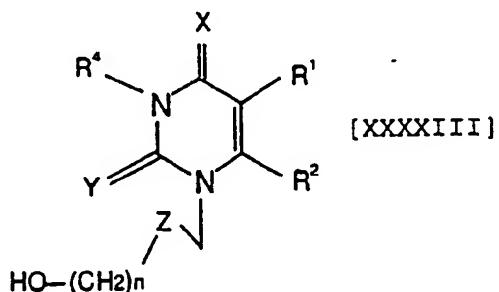


55 wherein R<sup>16</sup> have the same meaning as defined above and X<sup>8</sup> represents a halogen atom or sulfonyloxy group, in a solvent in the presence of a base to obtain the compound of the formula XXXIX above.

31 A process for the preparation of a compound represented by the following general formula XXXXI;



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, X, Y, Z and n have the same meaning as defined in claim 11, R<sup>17</sup> represents C<sub>1</sub> to C<sub>10</sub> alkyl or C<sub>6</sub> to C<sub>12</sub> aryl group and X<sup>9</sup> represents a sulfur or oxygen atom, which comprises reacting a compound represented by the following general formula XXXXIII;



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, X, Y, Z and n have the same meanings as defined in claim 11, with a compound represented by the following general formula XXXXX;

R<sup>17</sup>-N=C=X<sup>9</sup> [XXXXX]

wherein R<sup>17</sup> and X<sup>9</sup> have the same meanings as defined above, in a solvent in the presence of a base to obtain the compound of the formula XXXXI above.



Europäisches Patentamt  
European Patent Office  
Office européen des brevets



⑪ Publication number: 0 420 763 A3

⑫

## EUROPEAN PATENT APPLICATION

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㉓ Int. Cl. 5: C07D 239/60, C07D 239/54,  
C07D 239/56, C07D 239/47,  
A61K 31/505

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㉖ Designated Contracting States:  
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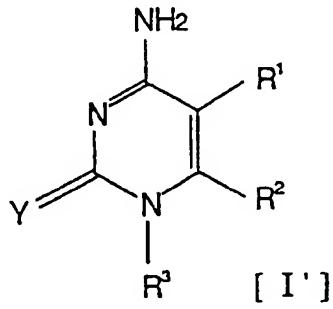
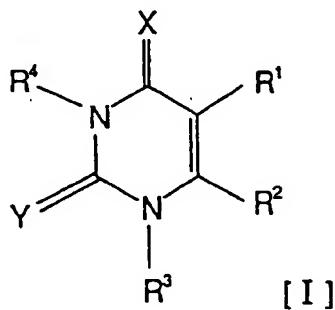
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㉛ 6-Substituted acyclopyrimidine nucleoside derivatives and antiviral agent containing the same as active ingredient thereof.

㉜ A 6-substituted acyclopyrimidine nucleoside derivative represented by the following general formula I or I';



wherein R<sup>1</sup> represents a hydrogen atom, halogen atom, alkyl, cycloalkyl, alkenyl, alkynyl, alkylcarbonyl,

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arylcarbonyl, arylcarbonylalkyl, arylthio or aralkyl group;

R<sup>2</sup> represents an arylthio, alkylthio, cycloalkylthio, arylsulfinyl, alkylsulfinyl, cycloalkylsulfinyl, alkenyl, alkynyl, aralkyl, arylcarbonyl, arylcarbonylalkyl or aryloxy group, those groups optionally substituted by one or more of substituents selected from a halogen atom, alkyl, halogenated alkyl, alkoxy, hydroxyl, nitro, amino, cyano and acyl groups;

R<sup>3</sup> represents a hydrogen atom, methyl, branched alkyl or -CH<sub>2</sub>-Z-(CH<sub>2</sub>)<sub>n</sub>-R<sup>5</sup> group where R<sup>5</sup> represents a hydrogen atom, halogen atom, hydroxyl, heterocyclic carbonyloxy, formyloxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, aralkylcarbonyloxy, arylcarbonyloxy, azido, alkoxy carbonyloxy, N-alkylcarbamoyloxy, N-arylcarbamoyloxy, N-alkylthiocarbamoyloxy, N-aryltiocarbamoyloxy, alkoxy, aralkyloxy, branched alkyl, cycloalkyl or aryl group, the alkoxy carbonyloxy to aryl groups mentioned above as R<sup>5</sup> optionally substituted by one or more substituents selected from a halogen atom, aryl, alkyl, alkoxy and halogenated alkyl groups, Z represents an oxygen, sulfur atom or methylene group, and n represents 0 or an integer of 1 to 5,

R<sup>4</sup> represents a hydrogen atom, alkyl or aralkyl group,

X represents an oxygen or sulfur atom,

Y represents an oxygen or sulfur atom,

provided that when R<sup>4</sup> and Z represent a hydrogen atom and oxygen atom respectively in the formula I R<sup>5</sup> does not represent a hydroxyl group,

or a pharmaceutically acceptable salt thereof, and an antiviral agent containing the derivative or the salt thereof as an active ingredient.



DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	TETRAHEDRON LETTERS, vol. 27, no. 1, January 1986, pages 113-116, Pergamon Press Ltd, Oxford, GB; I.T. KAY et al.: "A new synthesis of phenyl ketones by intramolecular "deoxybenzoylation" of enols and phenols" * Page 115, product 5 *	1,3-5	C 07 D 239/60 C 07 D 239/54 C 07 D 239/56 C 07 D 239/47 A 61 K 31/505
X	TETRAHEDRON, vol. 39, no. 23, December 1983, pages 3919-3921, Pergamon Press Ltd, Oxford, GB; M. SAKO et al.: "Reductive debromination of 5-bromouracils by 1-benzyl-1,4-dihydronicotinamide" * Page 3919, compounds 2d,2e *	1,3-6	
X	JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 19, no. 2, March-April 1982, pages 301-304; F. YONEDA et al.: "Synthesis of 2H-chromeno[2,3-d]pyrimidine-2,4(3H)-diones (10-oxa-5-deazaflavins)" * Page 301, table 1, compounds VIIa-VIIe *	1,3-5	
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 10, no. 3, May 1967, pages 304-311, Washington, DC, US; B.R. BAKER et al.: "Irreversible enzyme inhibitors. LXXVII" * Table I, compounds IV-VII,XV; table III, compound XXXVIII; table IV, lines 3,9; table V, line 14 *	1,3-6	
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 10, no. 3, May 1967, pages 316-320, Washington, DC, US; B.R. BAKER et al.: "Irreversible enzyme inhibitors. LXXX" * Table I, compounds II,XV,VII,XX-XXVI *	1,3-6	C 07 D 239/00 C 07 D 401/00 A 61 K 31/00
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 19, no. 1, January 1976, pages 71-98, Washington, DC, US; M. YOSHIMOTO et al.: "Correlation analysis of Baker's studies on enzyme inhibition. 2." * Table IX, compounds 38,39,54,57,65,66,70,71,75,80,83,90,94,97,104,109,110,121-123,126; table XII, compounds 1,2,10,16; table XVIII, compounds 11,13 *	1,3-6	
-/-			
The present search report has been drawn up for all claims			

Place of search	Date of completion of search	Examiner
The Hague	10 June 91	ENGLISH R.F.
CATEGORY OF CITED DOCUMENTS		
X: particularly relevant if taken alone		E: earlier patent document, but published on, or after the filing date
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P: intermediate document		
T: theory or principle underlying the invention		&: member of the same patent family, corresponding document

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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.5)			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)			
X	CHEMICAL ABSTRACTS, vol. 111, no. 17, 23rd October 1989, page 728, abstract no. 153828m, Columbus, Ohio, US; & JP-A-63 290 867 (SDS BIOTECH.) 28-11-1988 "Abstract" - - -	1,3-6				
X	CHEMICAL ABSTRACTS, vol. 106, no. 3, 19th January 1987, page 613, abstract no. 18608w, Columbus, Ohio, US; & JP-A-61 205 261 (SAGAMI CHEMICAL RESEARCH CENTER) 11-09-1987 "Abstract" - - -	1,3-6				
X	US-A-3 497 515 (H.M. LOUX) "Columns 1-2; column 18, examples 16,17" - - -	1,3-6				
X	WO-A-8 302 891 (HENKEL) "Page 2" - - -	1,3-6				
X	DE-A-2 126 148 (BAYER) "Page 3" - - -	1,3-6				
X	DE-A-2 142 317 (BAYER) "Pages 1-2" - - -	1,3-6				
P,X	EP-A-0 371 139 (MITSUBISHI KASEI) "Pages 2-5; page 25, example 198; pages 27-40 & WO-A-8 909 213 (Cat. D) - - - - -	1-12, 14-23,25, 26	TECHNICAL FIELDS SEARCHED (Int. Cl.5)			
The present search report has been drawn up for all claims						
Place of search	Date of completion of search	Examiner				
The Hague	10 June 91	ENGLISH R.F.				
CATEGORY OF CITED DOCUMENTS						
X: particularly relevant if taken alone						
Y: particularly relevant if combined with another document of the same category						
A: technological background						
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P: intermediate document						
T: theory or principle underlying the invention						
E: earlier patent document, but published on, or after the filing date						
D: document cited in the application						
L: document cited for other reasons						
&: member of the same patent family, corresponding document						